Carolina Witchmichen Penteado Schmidt
Fabiana Gatti de Menezes

Drug Therapy and Interactions in Pediatric Oncology

A Pocket Guide

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Preface

Professionals working in pediatric oncology must always remember they are working with a group of people who are undergoing physiological changes; this field requires broad knowledge of drugs, drug interactions, drug toxicities, and toxicity prevention.

There are few publications that deal specifically with drug interactions in pediatric oncologic patients. To fill this gap, we developed this book as a guide for pharmacists, physicians, nurses, researchers, and other health-care professionals involved in pediatric chemotherapy. Since chemotherapy schedules vary among hospitals and clinics, we selected protocols that form a benchmark in this field and are widely used in health-care systems. The book has an introduction related to drug interactions; also, another very important topic is examined: the enzyme complexes formed in the neonate, when they mature, and which chemotherapy drugs are metabolized by each enzyme complex. The appendix provides some important measures used in pediatric oncology, such as body surface area, how to calculate the dose of carboplatin, and the estimation of creatinine clearance. To sum up, this material is an important guide for oncology professionals who work with pediatric patients. It is an innovative handbook to help both professionals and students in residence programs on a daily basis.

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Abstract

Childhood cancer is a disease that can be considered to have a long survival time and major healing potential. Approximately 1–3 % of malignant tumors occur in children, taking into account most of the world's populations. In oncology, as well as in pediatric oncology, treatment generally consists of multiple drugs administered sequentially; these drugs have a narrow therapeutic window, the reason being that the therapeutic dose is close to the potentially toxic dose. Drug interactions may be programmed to diminish the toxicity, or to increase the therapeutic efficacy, or the interactions may be undesirable. The focus of this work is to guide professionals in the therapeutic chain and to present major drug interactions in pediatric oncology, by providing study material and consultation, contributing to our information in the search for better treatment and the fight against childhood cancer.

Acknowledgments, from Carolina Witchmichen Penteado Schmidt

To A.C. Camargo Cancer Center, for the immense increase in my professional life, with knowledge at the highest scientific level and always shared.

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Contents

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Academic experience in the fields of pharmacy, pediatrics, oncology, and hematology. Teaching for specialists such as pharmacists, physicians, and nurses. Author of an independent book that explains what cancer is for children (*What is Cancer? A Book for Kids*).

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with epidemiologic projects (real world data). Scientific and technical knowledge areas: pharmacology, pharmacotherapy, clinical protocols, clinical research, drug surveillance, pharmacoepidemiology, and pharmacoeconomics.

Abbreviations and Acronyms

AA	Arachidonic acid
AAG	α1-acid glycoprotein
ABC	ATP binding cassette
ADH	Antidiuretic hormone
AKR1	Aldo-Keto Reductase 1
ALDH	Aldehyde dehydrogenase
ALL	Acute lymphoblastic leukemia
ALOX5	5 – lipo – oxygenase
AML	Acute myeloid leukemia
Ara-C	Cytarabine
ASHSP	American Society of Health-System Pharmacists
ATRA	Trans-retinoic acid/tretinoin (not to be confused with isotretinoin)
AUC	Area under the curve
BFM	Berlin-Frankfurt-Münster
BLT_1/BLT_2	Leukotriene B4 receptors 1 and 2
BMT	Bone marrow transplant
BSA	Body surface area
CBC	Complete blood count
CDase	Ceramidase
CHL	Classical Hodgkin lymphoma
CML	Chronic myeloid leukemia
CNS	Central nervous system
COX	Cyclo-oxygenase
Crcl	Creatinine clearance
CYP450	Cytochrome P450
$CysLT_{1/}CysLT_2$	Cysteinyl leukotriene receptors 1 and 2
D	Day of treatment

DEXA	Dexamethasone
DOX	Doxorubicin
DOX-Fe^{2+}	Doxorubicin with Fe^{2+} complex
DP	Prostaglandin D2 receptor
dTMP	Deoxythymidine monophosphate
dUMP	Deoxyuridine monophosphate
EP_1-EP_4	Prostaglandin E receptors 1-4
FAB	French-American-British group of morphologists
FP	Prostaglandin F receptor
GFR	Glomerular filtration rate
GSH	Glutathione
HD	High dose
HL	Hodgkin lymphoma
HLNLP	Hodgkin lymphoma with nodular lymphocytic predominance
HR	High risk
ICCC	International Classification of Childhood Cancer
ICD	International Classification of Disease
IM	Intramuscular
INCA	Brazilian National Cancer Institute
IP	Prostacyclin receptor
IT	Intrathecal
IU	International Units
IV	Intravenous
K	Constant of proportionality
LP	Lymphocyte predominant
LPCAT	Lysophosphatidylcholine acetyltransferase
LT	Leukotriene
LTA_4H	Leukotriene-A4-hydrolase
LTC_4S	Leukotriene-C4-synthase
Lyso-PC	Lysophosphatidylcholine
MADIT	Methotrexate, cytarabine, and dexamethasone, all via IT route
MDR	Multidrug resistance gene complex
MIC	Morphological, immunological, and cytogenetic

MISPHO	Monza's International School of Pediatric Hematology-Oncology
MLC	Myosin light chain
MM-CK	Muscle creatine kinase
MT-CK	Mitochondrial creatine kinase
mtDNA	Mitochondrial deoxyribonucleic acid
MTX	Methotrexate
NADH	Nicotinamide adenine dinucleotide
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin lymphoma
OAT-1	Organic anion transporter-1
OCT-1	Organic cation transporter-1
PAF	Platelet activating factor
PAFR	Receptor of platelet activating factor
PGH_2	Prostaglandin H2
Ph	Philadelphia chromosome
PK	Pharmacokinetics
PLA2	Phospholipase A2
PMN	Polymorphonuclear
ROS	Reactive oxygen species
RSC	Reed-Sternberg cell
$S1P_1/SRR_2$	Sphingosine-1-phosphate receptors 1 and 2
SC	Subcutaneous
Scr	Serum creatinine
SK1/SK2	Sphingosine – kinase 1 or 2
SMase	Sphingomyelinase
TCR	T-cell receptor
TOPII	Topoisomerase II
TP	Thromboxane receptor
Trans reg proteins	Transcriptional regulatory proteins
TROP	Troponin
TX	Thromboxane
WBC	White blood cell
β1ADR	Adrenergic β1 receptor

Chapter 1
Introduction

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Childhood cancers are diseases that can be considered to have high survival times and major healing potential, but despite progress in oncology, there is still a group of patients who will not be cured [12, 70, 71, 78].

Childhood cancers have many common characteristics that distinguish them from tumors in adults [35, 45, 72]. Typical tumors in children seem to arise from embryonal tissues arrested at

different stages of maturation; for example: retinoblastoma, hepatoblastoma, and Wilms tumor. Many morphologic features of some childhood malignant tumors, such as clear cell sarcoma of kidney, malignant rhabdoid tumor, and melanotic neuroectodermal tumor, are not encountered in those occurring in adults. Cancer in this specific group is also typified by the frequent occurrence of undifferentiated tumors, also termed "small round cell tumours", such as the Ewing family of tumors, Burkitt's lymphoma, and several acute leukemia types. Childhood neoplasms are also rarely preceded by precursor lesions [72].

Although childhood cancer is rare, it is a leading cause of death in developed countries. Cancer survival in adolescents or young adults is worse than that in children who have biologically similar cancers, probably because of the intensive treatment protocols that have been developed mainly for children. Detection of childhood cancer depends on the primary health care provided, and in most developing countries, cancer is not a public health priority; priorities in these countries are usually infectious diseases. Childhood cancer incidence rates are normally higher in developed than in developing countries; in some developing countries, many children who have cancer are never diagnosed, or are diagnosed too late, or treatment is limited, and cases are often unreported. The majority of children, and approximately 80 % of children with cancer, live in developing countries. Mortality rates are lower in developed countries, despite higher incidence rates, reflecting better diagnosis and treatment [71, 72, 76].

The development of diagnostic methods such as computerized tomography, magnetic resonance imaging, and nuclear medicine scans has increased the accessibility and the precision of diagnosis; probably this explains, in part, the increase in the incidence of central nervous system (CNS) tumors observed in the United States and Europe in recent decades, and also the low incidence rates in developing countries [72].

Some pediatric malignancies are seen predominantly in pre-school children; others, such as bone tumors, non-Hodgkin lymphomas, most cases of Hodgkin disease, and different epithelial tumors, occur in older children [72].

Most cancers occurring in adults are carcinomas and are classified by the International Classification of Disease (ICD), in which groups are classified by site; in contrast, cancers in childhood are histologically very different and some types can occur in many different sites, probably the most used classification of childhood cancer is the ICCC (International Classification of Childhood Cancer) [73]. There are 11 main groups in this classification: leukemias; lymphomas and other reticuloendothelial neoplasms; brain and spinal tumors (including non-malignant tumors); sympathetic nervous system tumors; retinoblastoma; renal tumors; hepatic tumors; bone tumors; soft-tissue sarcomas; germ-cell, trophoblastic, and other gonadal neoplasms; and carcinomas and other epithelial neoplasms [70, 73].

The financial cost of cancer is substantial, and research has shown that cancer has the most devastating economic impact, of any cause of death, in the world. It is not possible to say the worldwide economic costs of cancer exactly, but some of the total costs of cancer have been estimated to be as high as US$895 billion worldwide [71].

1.1 Childhood Cancer in Europe

About 15,000 children aged between 0 and 14 years are diagnosed with cancer every year in Europe, although this age group represents only 1 % of all cancers diagnosed [76]. In Germany, for example, the total annual incidence rate for cancer in patients more than 80 years old is currently approximately 200–300 times higher than that for children under 15 years old [81].

Primary tumours of the CNS are the second most common cancer in children aged 0–14 years in Europe, comprising over 20 % of cases [95].

European populations differ considerably in cancer survival, implying inequality of access to treatment for diseases in children, which are typically highly curable [76, 77, 96].

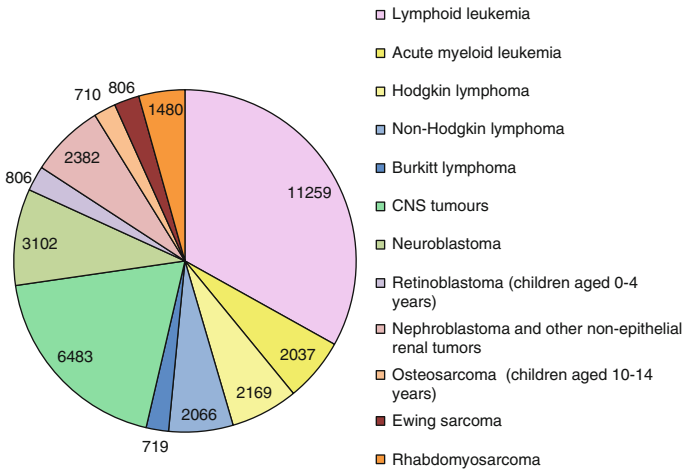

FIGURE 1.1 Incidence in Europe (countries participating in EUROCARE-4) of common cancers diagnosed in children (0–14 years) between 1995 and 2002 (*Source*: Based on information from Gatta et al. [76])

Between the years 1995 and 2002 in Europe, 70,579 cases of cancer in children and young adults were registered; most of the cases (26.3 %) were in children between 0 and 4 years old [76].

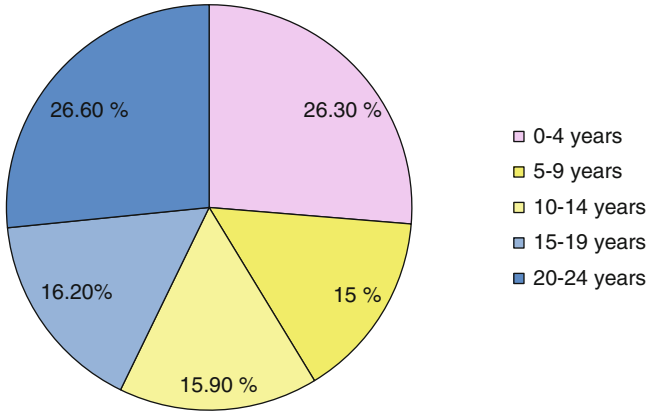

FIGURE 1.2 Cancer cases in young Europeans (0–24 years), diagnosed in 1995–2002 in Europe (countries participating in EUROCARE-4), according to age (*Source*: Based on information from Gatta et al. [76])

Survival rates for childhood cancer vary throughout Europe, with lower 5-year survival rates observed in Eastern Europe compared with other regions. The survival rates for Northern and Central Europe are similar to those found in the United States [71, 75].

In Europe, the best 5-year survival rate for children between 0 and 14 years old diagnosed with acute lymphoblastic leukemia (ALL)—which is the most frequent hemato-oncological disease in children worldwide—in the years 2005–2009, was in Germany, with 91.8 % of these children with 5-year survival, followed by Austria, with 91.1 %. These rates have shown that the survival of children with ALL in Europe is considerably higher than that in developing countries [75].

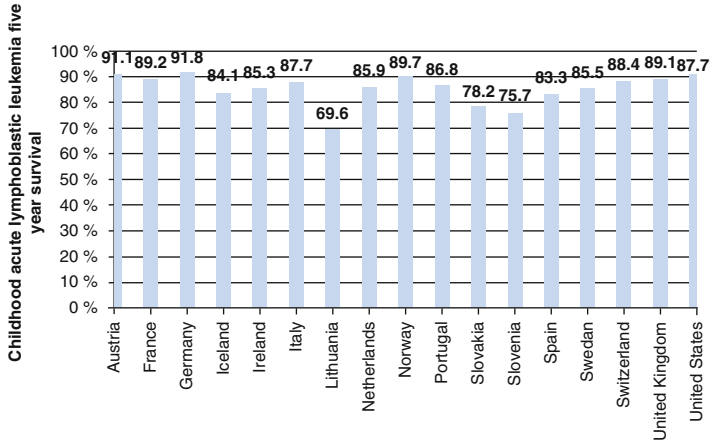

FIGURE 1.3 Estimates of childhood acute lymphoblastic leukemia (ALL) 5-year survival for children between 0 and 14 years, diagnosed in 2005–2009, in Europe (*Source*: Based on World Health Organization information [75])

In Europe, survival at 5 years from diagnosis for children between 0 and 14 years, for all cancers combined, is generally good, with 79 % surviving in the years 2005–2007, up from the rate in 1999 to 2001 (76 %); however, no progress has been achieved in pediatric malignancies with the poorest prognosis, and childhood cancer remains a public health issue [77].

Differences in survival were observed between countries grouped by the level of socio-economic development, according to Eurocare research. There are still disparities in the survival of children and adolescents with cancer across Europe; survival in Eastern Europe is generally 10–20 % lower than in Western Europe, and these disparities become larger for pediatric cancers with poor outcomes [72, 77, 96].

Among the predominantly white populations of Western Europe, the incidence of Hodgkin lymphoma appears to be lowest in colder regions of higher latitude; Eastern Europe is a region of intermediate incidence; nodular sclerosis is relatively rare, and the increase at ages between 10 and 14 years is not as steep as in the west of Europe [73].

In Great Britain, between the years 2006 and 2008, the most common type of childhood cancer was leukemia, with 262 cases in boys and 205 cases in girls; followed by brain, other CNS, and intracranial tumors, with 219 cases in boys and 193 cases in girls. The incidence and age distribution of ALL among children of South Asian ethnic origin are very similar to those among whites, although children of South Asian ethnic origin have a much higher incidence of Hodgkin lymphoma than white children; this can be explained by a higher incidence of the mixed cellularity subtype before age 10 years. Children of West Indian descent in Great Britain have a low relative frequency of brain tumors, and the relative frequency among children of Asian descent in Great Britain is also low, as opposed to the relative frequency of cancers of the sympathetic nervous system, in which there is no sign of any variation between ethnic groups [73, 78]. Children of West Indian descent in Great Britain also have a relatively high frequency of Wilms tumor compared with that in white children, in whom it represents 5–7 % of all childhood cancers [73].

For Hodgkin lymphoma, children and siblings of patients with this disease have a significantly increased risk of developing the disease [81].

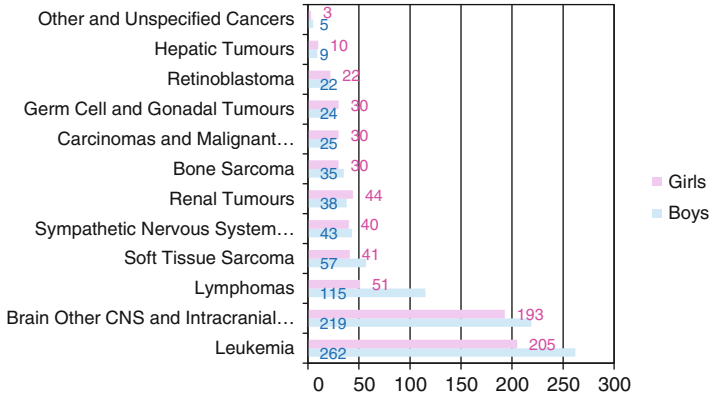

FIGURE 1.4 Incidence of cancer in children between 0 and 14 years old in Great Britain, diagnosed in 2006–2008 (*Source*: Based on information from Cancer Research UK [78])

Hepatoblastoma is one of the rarer embryonal tumors; in general, cases are diagnosed in the first few years of life. In England and Wales, one-third of these tumors are diagnosed in infancy, and 85 % before the fifth birthday, and they appear to have very little geographic variation. The incidence rate worldwide is around 1 case per million people. In contrast, hepatocellular carcinoma has much more geographic variability, and most cases occur in children 10–14 years old. In Europe this disease is rare in childhood, occurring with about half the frequency of hepatoblastoma [73].

1.2 Childhood Cancer in North America

According to data from the U.S. Cancer Statistics Working Group, for ages 0–19, the invasive cancer incidence count showed that there were 74,104 cases of childhood cancer, classified by the ICCC, between the years 2008 and 2012 in the United States; thus, the incidence rate was 976.5 (this incidence is an age-specific rate, with the number of cases or deaths in a specified age category divided by the population in the specified age category, then multiplied by 1 million). Cancers with fewer than 16 cases reported are

suppressed in this data. The most common diseases were categorized as leukemias and myeloproliferative and myelodysplastic diseases, with 19,647 cases between the years 2008 and 2012, an incidence rate of 252.5 per 1 million of children. The most common cancerous diseases in children under 1 year old in the United States were neuroblastoma and other peripheral nervous cell tumors, with 1133 cases between the years 2008 and 2012, followed by leukemias and myeloproliferative and myelodysplastic diseases, with 1021 cases; the total invasive cancer incidence rates in children under 1 year old was 5254 [70].

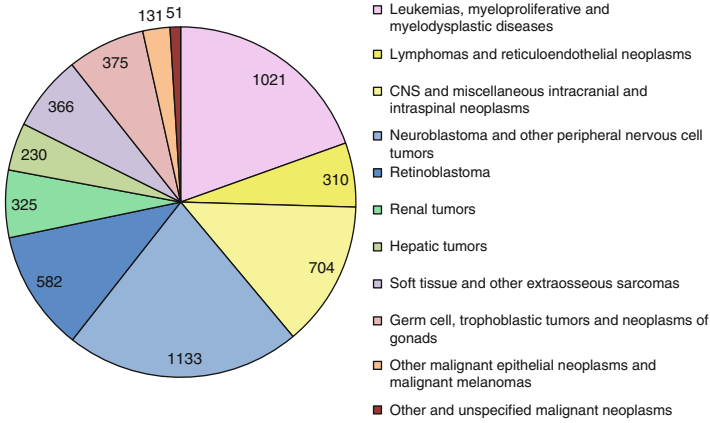

FIGURE 1.5 Incidence of cancer in children under 1 year of age in the United States between 2008 and 2012 (*Source*: Based on information from the U.S. Cancer Statistics Working Group [70])

The incidence of invasive cancer, classified by the ICCC, for children between 1 and 4 years old in the United States, was 18,182 cases between the years 2008 and 2012, with an incidence rate of 227.1 per million. The most common diseases were leukemias and myeloproliferative and myelodysplastic diseases, with an incidence of 7426 cases, an incidence rate of 92.7 per million, followed by CNS and miscellaneous intracranial and intraspinal neoplasms, with an incidence of 3614 cases, an incidence rate of 45.1 per million [70].

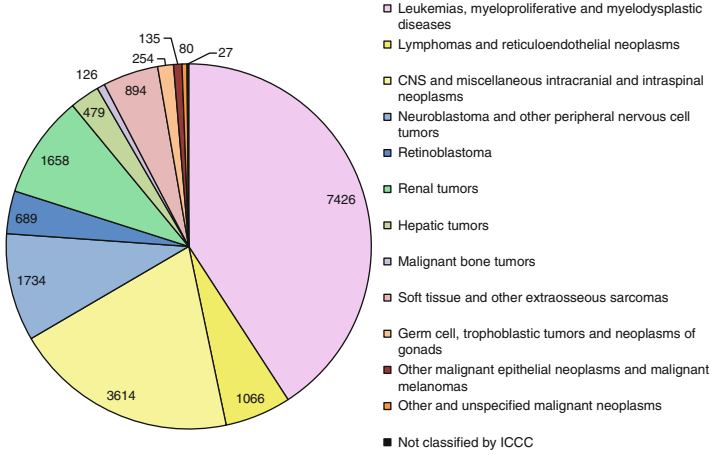

FIGURE 1.6 Incidence of cancer in children 1–4 years of age in the United States between 2008 and 2012 (*Source*: Based on information from the Cancer Statistics Working Group [70]). *Cancers with fewer than 16 cases reported are suppressed in this data

The incidence of invasive cancer, classified by the ICCC, for children between 5 and 9 years old in the United States, was 12,767 cases between the years 2008 and 2012, with an incidence rate of 127.2 per million. The most common diseases were leukemias and myeloproliferative and myelodysplastic diseases, with an incidence of 4332 cases, an incidence rate of 43.2 per million, followed by CNS and miscellaneous intracranial and intraspinal neoplasms, with an incidence of 3472 cases, an incidence rate of 34.6 per million [70].

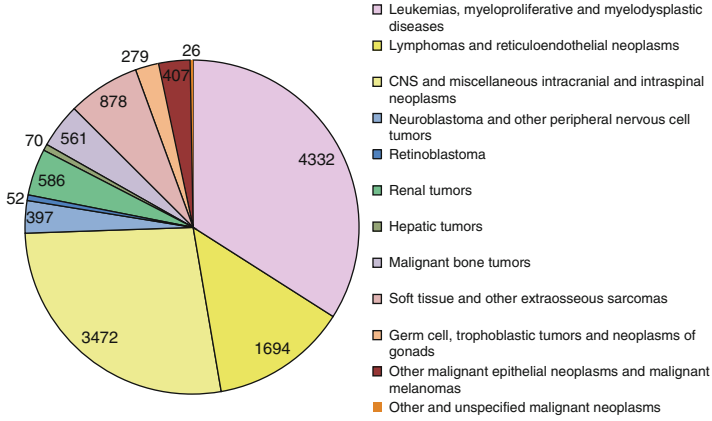

FIGURE 1.7 Incidence of cancer in children 5–9 years of age in the United States between 2008 and 2012 (*Source*: Based on information from the Cancer Statistics Working Group [70]). *Cancers with fewer than 16 cases reported are suppressed in this data

The incidence of invasive cancer, classified by the ICCC, for children between 10 and 14 years old, in the United States, was 14,060 cases between 2008 and 2012, with an incidence rate of 137.2 per million. The most common diseases were leukemias and myeloproliferative and myelodysplastic diseases, with an incidence of 3331 cases, an incidence rate of 32.5 per million, followed by CNS and miscellaneous intracranial and intraspinal neoplasms, with an incidence of 2758 cases, an incidence rate of 26.9 per million. Different from other age groups, the data for children between 10 and 14 years old with CNS and miscellaneous intracranial and intraspinal neoplasms was very similar to the data for children in this age group with lymphomas and reticuloendothelial neoplasms; this specific group had an incidence of 2646 cases, an incidence rate of 25.8 per million [70].

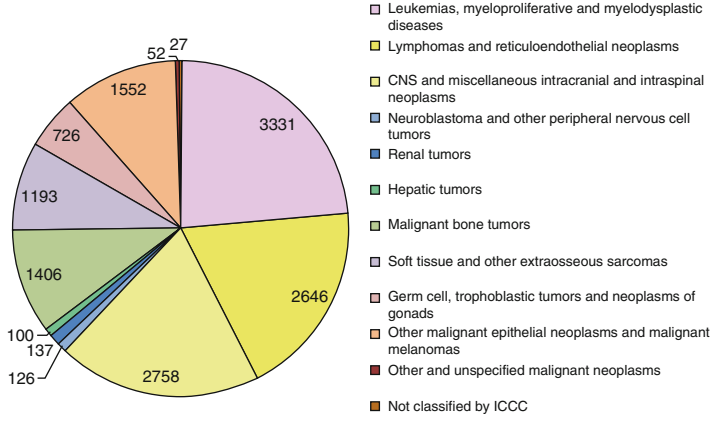

FIGURE 1.8 Incidence of cancer in children 10–14 years of age in the United States between 2008 and 2012 (*Source*: Based on information from the Cancer Statistics Working Group [70]) *Cancers with fewer than 16 cases reported are suppressed in this data

The incidence of invasive cancer, classified by the ICCC, for children and adolescents between 15 and 19 years old in the United States, was 23,841 cases between the years 2008 and 2012, with an incidence rate of 219.8 per million. The most common diseases were lymphomas and reticuloendothelial neoplasms, with an incidence of 5520 cases, an incidence rate of 50.9 per million, followed by leukemias and myeloproliferative and myelodysplastic diseases, with an incidence of 3537 cases, an incidence rate of 32.6 per million [70].

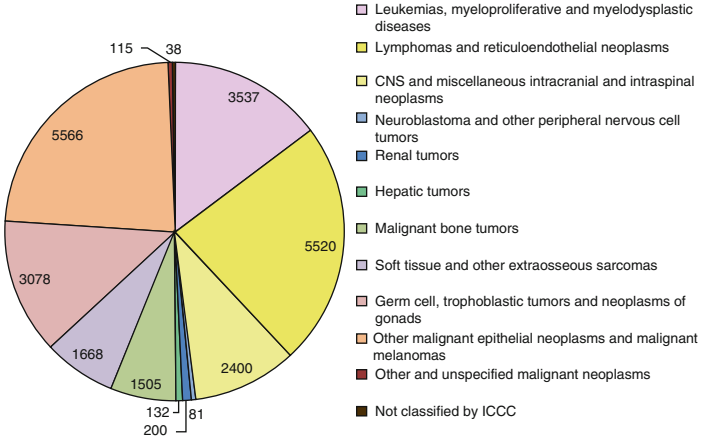

FIGURE 1.9 Incidence of cancer in children and adolescents 15–19 years of age in the United States between 2008 and 2012 (*Source*: Based on information from the Cancer Statistics Working Group [70]). *Cancers with fewer than 16 cases reported are suppressed in this data

Mortality rates for childhood cancers, in general, mainly leukemia, have sharply declined over the past 40 years in economically developed countries such as the United States and Canada, due to improved diagnosis, treatment, and reporting methods [71, 79].

The incidence of ALL among black children in the United States is only half that among white children, largely because of a much reduced early childhood peak. The incidence of brain tumors in this same group of children is lower than in white children in the United States; and black children in the United States have a lower incidence of sympathetic nervous system tumors than white children in infancy, but rates are similar thereafter. The highest incidence of Wilms tumor in childhood occurs among black children, both in Africa and in the United States [73].

High incidence rates of acute myeloid leukemia (AML) have been recorded among the Hawaiian population, with an incidence rate of 11–14 cases per million people. The reasons probably include a genetic predisposition. Acute myeloid leukemia usually has an incidence rate of 4–10 cases per million people in other populations, with little variation between regions of the world or ethnic groups, and when there is a high relative frequency of AML, generally there is, consequently, a lower incidence of ALL [84].

Among the predominantly white populations of North America, the incidence of Hodgkin lymphoma in childhood appears to be lowest in colder regions of higher latitude; the predominant subtype is nodular sclerosis, accounting for about two-thirds of registrations in the United States; black children have a slightly higher incidence of Hodgkin lymphoma than white children at ages between 0 and 9 years, and a lower rate at ages between 10 and 14 years; rates of nodular sclerosing histology are similar in the two ethnic groups, but lymphocyte predominance is more common among black children [73].

In California and Hawaii, the incidence of Wilms tumor in children whose descent is of East Asian ethnic origin is very low [73].

Hepatoblastoma appears to have very little geographic variation in incidence, at around 1 per million worldwide; in contrast, hepatocellular carcinoma has much more geographic variability, and most cases occur in children 10–14 years old; in the United States, as in Europe, it is rare in childhood, occurring with about half the frequency of hepatoblastoma [73].

According to a health care costs and utilization project in 2009 in the United States, there were 94,600 hospitalizations of children under 18 for whom the primary cause of hospitalization was cancer, representing 5.2 % of hospitalization costs for children (excluding newborns), and a total cost of 859.8 million dollars. The most common disease was leukemia, which showed a cost of 385.8 million dollars in 2009, followed by brain and CNS cancers, which showed a cost of 154.8 million dollars [51].

1.3 Childhood Cancer in Latin America

According to data from the Brazilian National Institute of Cancer (INCA), approximately 1–3 % of all malignant tumors occur in children, taking into account the majority of the world population [41].

High incidence rates of Hodgkin lymphoma in childhood have been reported from some registries in South America, but even when the total incidence is relatively low, the 10- to 14-year age group has not provided a very high proportion of cases [58, 71, 73].

Brazil is a developing country with a high proportion of young people, and childhood cancer is considered to be the most important cause of death in children aged between 0 and 14 years; there is evidence that this fact is due to the current policies of prevention, which focus on other children's diseases; this is unlike findings in developed countries, where pediatric cancer is the second leading cause of death [40]. In Brazil, in 2005, the deaths of children and adolescents aged between 1 and 19 years due to cancer corresponded to 8 % of all deaths, and cancer was the second leading cause of infant death; the leading cause of infant death was due to external

factors (such as accidents and violence), and childhood cancer was the leading cause of death due to disease [40].

In Latin America, at least 3000 cancer deaths in children under 15 years old could be avoidable through the widespread adoption of adequate and modern treatment [79].

In Venezuela, the estimated overall 5-year survival rate for childhood cancer is as low as 40–60 % [71].

In Brazil, there are health policies focused on basic child care, such as breastfeeding, child protection from violence, and children's nutrition; Brazil is considered to be a country in development, and child health policy is focused on diseases such as malnutrition and health problems arising from poor sanitation [39].

The diagnosis and treatment of cancer represent a significant proportion of the investments in health care around the world [37].

In Latin America, the cure rate for childhood cancer remains considerably lower than that in developed countries, despite some progress. Childhood cancers accounted for >6000 deaths in the ten major countries of Latin America in 2005, and the current rates are more than twice those of North America [79].

1.4 Childhood Cancer in Africa

There is large socio-economic diversity in Africa [71], where cancer is an emerging public health problem. About 681,000 new cancer cases and 512,400 cancer deaths occurred in Africa in 2008. There is a projection to 1.28 million new cases and 970,000 cancer deaths by 2030, due to population aging and population growth [71].

Although ALL is the most common disease in pediatric hemato-oncology worldwide, the incidence of childhood ALL in sub-Saharan Africa is considerably low, with little or no sign of a peak in the age-incidence curve, and the incidence rates of neuroblastoma in this region are the lowest found [73]. In developing countries, but especially in the sub-Saharan region of Africa, the incidence of retinoblastoma is generally higher than other countries [73].

The risk of Burkitt's lymphoma is highest in tropical Africa, due to the association of this lymphoma with infection by the Epstein-Barr virus and the intense stimulation of immunity caused by malaria; the African type of Burkitt's lymphoma is also associated with a chromosomal translocation that deregulates the expression of the c-myc oncogene. In children who have immunodeficiency, the Epstein-Barr virus is probably also implicated in Hodgkin disease, non-Hodgkin lymphomas, nasopharyngeal carcinoma, and other cancers [72, 73]. Most hepatic carcinomas occurring with the highest frequencies in sub-Saharan African registries are due to the Hepatitis B and C viruses [72].

In Northern Tanzania, the suppression of malaria by regular chemoprophylaxis reduced the incidence of Burkitt's lymphoma, with a rebound to previous levels when the program was ceased [73].

Black children seem to have a higher propensity to develop Wilms tumor and osteosarcoma. One very rare type of Burkitt's lymphoma is one of the most common tumors registered in some countries of sub-tropical Africa [72, 73].

The incidence of childhood Kaposi's sarcoma has increased considerably in parts of Africa where the incidence of AIDS is extremely high [73].

Retinoblastoma seems to be more common in African children than elsewhere [72].

In South Africa, tuberculosis accounted for the highest number of reported deaths; 58,051 cases were reported. In 2013, the list of the 20 most commonly reported causes of death in South Africa showed malignant neoplasms in defined; secondary and unspecific sites to be in the twentieth position of reported deaths, with 12,001 deaths; only 2.6 % of all deaths were due to the 20 most common causes. In the ten leading underlying natural causes of death for broad age groups in South Africa in 2013, respiratory and cardiovascular disorders specific to the perinatal period were the most important causes of death in children less than 1 year old, with 14.3 % of total causes of natural death reported in this age group. For children between 1 and 14 years old, the most

important cause of natural death was intestinal infectious disease, at 14.1 % of the total of deaths reported [74].

The estimated overall 5-year survival rates for childhood cancer are as low as 40–60 % in Egypt, 30 % in Morocco, and 5–10 % in Senegal [71].

Neuroblastoma is very rare in central Africa [72].

Despite the high and growing rates of cancer in Africa, cancer receives low public health priority, because of limited resources and other public health problems, such as AIDS, malaria, and tuberculosis [71].

1.5 Childhood Cancer in Asia

In Japan, in the years 2004–2006, cancer was the fourth leading cause of death among children aged 0–14 years; rates of childhood cancer mortality in Japan have shown similar and even more favorable results than those in the European Union [79].

The mortality rate for all childhood cancers during 2010–2013 in Japan was 19.9 per 1 million people for boys and 17.5 per 1 million people for girls; mortality caused by childhood cancer decreased significantly from 1980 to 2003 for boys and from 1980 to 2001 for girls. Three hundred Japanese children died from cancer in 2013, and leukemia was the most common diagnosis, at 33.7 % of all childhood cancer cases, followed by CNS tumors, at 29.3 % of all cases [82].

In Asia, Wilms tumor in children is very rare, with under 5 cases per million people found throughout East Asia, and the low incidence is more marked among older children; 25–40 % of the total incidence occurs in infants aged under 1 year. Ewing sarcoma of bone is rare in Asia too, and neuroblastoma rates are also substantially lower in this continent than elsewhere. The lowest incidence of Wilms tumor is in India, but this could be due to under-ascertainment, as the relative frequency is similar to that in Western countries [72, 73].

In Hong Kong, according to registries, hepatic carcinomas that occur with the highest frequencies are due to the Hepatitis B and C viruses [72].

The estimated overall 5-year survival rates for childhood cancer in Vietnam and Bangladesh are as low as 5–10 % [71].

In the predominantly white populations of Europe, the Americas, and Oceania, as well as white population of Eastern Asia, around a third of all childhood cancers are leukemia, with annual incidence rates of 35–50 cases per million people; a similar relative frequency is found in India, though the incidence is lower, possibly because of under-ascertainment. A marked peak for ALL in early childhood has appeared in Kuwait [73].

Azerbaijan and Kazakhstan have had some declines in childhood cancer mortality over recent years, mainly leukemias, but their childhood cancer mortality rates remain higher than those in more developed countries [79].

In Beijing, research has shown that the incidence rate of childhood cancer from 2002 to 2009 was 106.47 cases per million; the most common diagnoses were leukemia (39.64 %), followed by CNS tumors (17.90 %), and then lymphoma (7.14 %) [80].

1.6 Childhood Cancer in Central America

One large study carried out in Central America found that the 3-year survival rate of childhood cancer ranged from 48 to 62 %, with pronounced variations across eight national hospitals in seven countries [71].

Pediatric cancer patients are not receiving high public health priority and they have a high risk of severe under-treatment because of lack of resources and organizational facilities [83].

High incidence rates of Hodgkin lymphoma in childhood have been reported from some registries in Central America, but even when the total incidence is relatively low, the 10- to 14-year age group has not shown a very high proportion of cases [73].

Mortality rates for childhood cancer in general, mainly leukemia, have sharply declined over the past 40 years in economically developed countries, due to improved diagnosis, treatment, and reporting methods, but Mexico, the country that had the highest rates of childhood cancer deaths in 2005, did not have a pediatric oncologist, up to the year 2000, in 13 of its 32 states [71, 79].

In a study of one network of centers working in the field of hemato-oncology in Central America and the Caribbean (specifically Costa Rica, Cuba, El Salvador, Guatemala, Honduras, Nicaragua, and the Dominican Republic, where the hospitals that were active members of Monza's International School of Pediatric Hematology–Oncology (MISPHO) could be considered to represent the whole of the resources available for childhood cancers in their country), established in 1996 under the auspices of MISPHO, there was a total of 2214 children with cancer. The study participants activated a protocol for the retrospective epidemiological evaluation of all incident cases diagnosed with cancer in the period between the years 1996 and 1999, to provide a register of basic demographic and clinical data [83].

Most cases of hemato-oncological disorders were reported in El Salvador, with 427 children (252 boys and 175 girls) followed by Nicaragua, with 175 cases in boys and 131 in girls, a total of 306 cases [83].

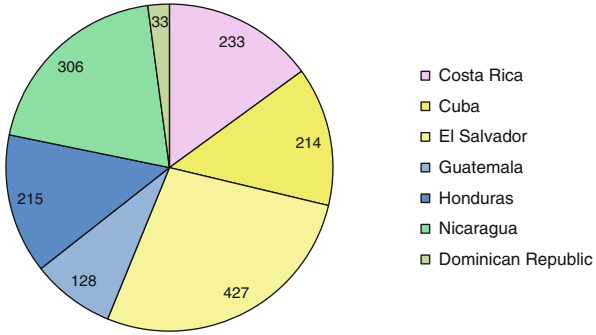

FIGURE 1.10 Incidence of hemato-oncological disorders for the 2214 evaluable cases diagnosed with childhood cancer in the period 1996–1999 in Central America and the Caribbean (*Source*: Based on information from Valsecchi et al. [83])

The incidence of solid tumors for the 2214 evaluable cases diagnosed with childhood cancer in the period 1996–1999 in Central America and the Caribbean did not include Costa Rican rates, which were not provided. The country with the most cases was El Salvador, with 633 children diagnosed between 1996 and 1999, followed by Nicaragua, with 463 cases [83].

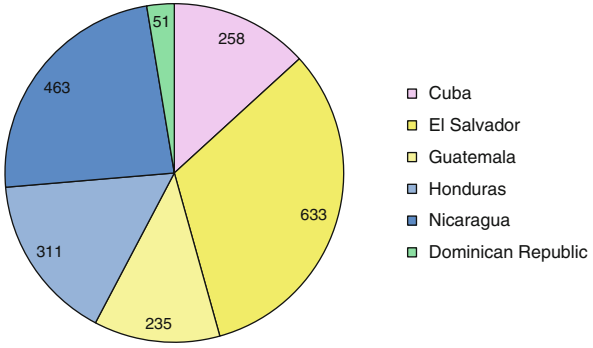

FIGURE 1.11 Incidence of solid tumors for the 2214 evaluable cases diagnosed with childhood cancer in the period 1996–1999 in Central America and the Caribbean (*Source*: Based on information from Valsecchi et al. [83])

One big problem during the treatment of childhood cancers is the drop-out rate. There was a considerable drop-out rate in the 2214 evaluable cases diagnosed with cancer in the period 1996–1999 in Central America and the Caribbean. There were 65 deaths, 39 with hemato-oncological disorders and 26 with solid tumors [83].

Table 1.1 Drop-out rates in patients with hematological diseases among 2214 evaluable cases diagnosed with cancer in the period 1996–1999 in Central America and the Caribbean

Country	Number of patients	Number of drop-outs	Percentage of drop-outs (%)
Costa Rica	233	7	3
Cuba	214	2	0.93
El Salvador	427	115	26.93
Guatemala	128	30	23.43
Honduras	215	70	32.55
Nicaragua	306	37	12.09
Dominican Republic	33	11	33.33

Source: Based on information from Valsecchi et al. [83]

Table 1.2 Drop-out rates in patients with solid tumors among 2214 evaluable cases diagnosed with cancer in the period 1996–1999 in Central America and the Caribbean

Country	Number of patients	Number of drop-outs	Percentage of drop-outs (%)
Cuba	44	1	2.27
El Salvador	236	77	32.62
Guatemala	107	47	43.92
Honduras	96	39	40.62
Nicaragua	157	39	24.84
Dominican Republic	18	2	11.11

Source: Based on information from Valsecchi et al. [83]

1.7 Childhood Cancer in Oceania

In Oceania, the risk of Burkitt's lymphoma is highest in Papua New Guinea, due to the association of this lymphoma with infection by the Epstein-Barr virus and the intense stimulation of immunity caused by malaria. In children who have immunodeficiency, the Epstein-Barr virus is probably also implicated in Hodgkin disease, non-Hodgkin lymphomas, nasopharyngeal carcinoma, and other cancers [72, 73]. Among the predominantly white populations of Oceania, the incidence of Hodgkin lymphoma appears to be lowest in colder regions of higher latitude [73, 84].

Cancer was the second leading cause of death among children aged 1–14 years in Australia between the years 2004 and 2006 [79].

Rates of childhood cancer mortality in Oceania have shown similar and even more favorable results than those in the European Union [79].

Among the predominantly white populations of Oceania, most childhood cancers are leukemias—about a third—and the age-standardized rate is 35–50 per million children [84].

Estimates of 5-year survival in childhood ALL for children between 0 and 14 years, diagnosed in the years 2005–2009, showed 88.6 % of children with a 5-year survival in Australia and 89.3 % in New Zealand [75].

The highest rates of malignant melanoma have been found in Oceania; the incidence rate in most childhood populations is about 1 case per million children. Some registrations may have been cases that were nonmalignant, although, in New Zealand, the incidence of malignant melanoma, confirmed by pathology, was still double that in the white populations of the northern hemisphere; this probably occurs because of the high exposure to sunlight in predominantly fair-skinned populations; New Zealand also has the highest incidence of malignant melanoma in adults [84]. Mortality rates for childhood cancer, mainly leukemia, have sharply declined over the past 40 years in New Zealand [71, 79].

High incidence rates of AML have been recorded among the Maori population of New Zealand, with an incidence rate of 11–14 cases per million people. The reasons for this high rate probably

include a genetic predisposition. Acute myeloid leukemia usually has an incidence rate of 4–10 cases per million people in other populations, with little variation between regions of the world or ethnic groups, and when there is a high relative frequency of AML, generally there is, consequently, a lower incidence of ALL [84].

1.8 Pharmacological Treatment in Childhood Cancer

In oncology, as well as in pediatric oncology, pharmacological treatment generally consists of multiple drugs administered simultaneously; apart from those medications with a narrow therapeutic window, which makes the therapeutic dose near the potentially toxic dose. Drug interactions can be programmed to decrease toxicity or to increase therapeutic efficacy, or the interactions may be undesirable. In clinical practice, relevant interactions are those that have a rapid onset of action (within 24 h), those that have a high probability of risk to the patient's life, and that interactions which are well documented [19, 104].

Chemotherapeutic drugs are part of the group of most toxic prescription medications and there is relatively little published about drug interactions of high importance in pediatric oncology. Chemotherapeutic drugs are part of a group of special concern because of their narrow therapeutic index and high lethality; however, because chemotherapy drugs are usually administered together, through certain protocols, this complicates the analysis of drug interactions and the identification of the specific agents involved in any interaction [37].

Interactions between chemotherapeutics and other medicines can cause small changes in the pharmacokinetics or pharmacodynamics of the chemotherapeutic agent and may significantly change the chemotherapy efficacy or toxicity [57, 104, 105].

Drug interaction is defined as the modulation of a drug's activity, altering its pharmacological activity, after the administration of another drug. Drug interactions are frequent in oncology, and with the increase in the number of molecules

used in recent years, there has been an increase in the potential for interactions, and with the increase of drugs administered simultaneously, the incidence of drug interactions also increases [19].

With the knowledge that childhood cancers present differences from adult cancers—consisting of histological differences, differences in the primary location, different clinical behaviors, usually shorter latency periods, and fast growth—but with better response to chemotherapy [23], this book aims to provide, for professionals working in pediatric oncology, a guide regarding possible drug interactions that have clinical significance.

Chapter 2
The Main Diseases in Pediatric Hemato-oncology

List of tables

2.1 Hodgkin Lymphoma (HL)

This form of cancer originates in lymph nodes, arising when a lymphocyte becomes a malignant cell [19, 97].

HL represents approximately 30 % of all lymphomas in the United States, with an age peak between 15 and 30 years [17, 97]. It is characterized by the proliferation of giant cells, bi- or multinucleated, called Reed-Sternberg cells (RSCs) — or their variants — that characterize 1 % of cells from the lymphoma, while the rest are comprised of inflammatory cells. The RSCs are clonal B-lymphocytes, which do not produce immunoglobulin nor possess functional B-receptors. They can be classified as classical (CHL) or HL with nodular lymphocytic predominance (HLNLP). In HLNLP the predominant cell (LP cell/popcorn cell) is a variant of the RSC, the lymphocyte predominant cell

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(LP cell/ popcorn cell). The two classifications are differentiated by immunohistochemistry. CHL: CD15+, CD20-, CD30+, CD45-; HLNLP: CD15-, CD20+, CD30-, CD45+ [17].

Hodgkin lymphoma is one of a few neoplasms that are similar in children and adults from a biological standpoint. Children tend to evolve well, but attention must be paid to later complications such as secondary leukemia, pulmonary fibrosis, heart failure, infertility, and secondary neoplasms, features which should, therefore, limit the doses of chemotherapy and radiotherapies [17].

There are strong correlations between Epstein-Barr virus infection and HL [72, 73, 97].

The treatment in childhood usually consists of a combination of chemotherapy and low-dose radiotherapy. In this combined modality treatment, survival is achieved in up to 90 % [97].

2.2 Non-Hodgkin Lymphoma (NHL)

Non-Hodgkin lymphoma is a group of diseases that comprise the Burkitt, large-cell, and lymphoblastic subtypes, as classified according to the World Health Organization system. Lymphoblastic lymphoma represents approximately 30 % of all pediatric NHL cases and the vast majority consists of advanced-stage lymphoblastic lymphoma with a precursor T-cell immunophenotype [98].

Non-Hodgkin lymphoma comprises 6 % of the total of childhood cancers, and unlike NHL in adults, childhood NHL is frequently high grade (in adults it is generally low or intermediate grade). It can be divided into three specific categories: mature B-cell (including Burkitt, Burkitt-like lymphoma, and diffuse large B-cell lymphoma); lymphoblastic lymphoma (mostly precursor T-cell); and anaplastic large-cell lymphoma (mature T-cell or null-cell). Currently, the cure rate for childhood NHL is 90 % [99].

2.3 Chronic Myeloid Leukemia (CML)

Chronic myeloid leukemia is a malignant clonal disease characterized by the excessive proliferation of cells of myeloid lineage, which forms the chronic phase; this is followed by the progressive loss of cellular differentiation, forming the accelerated phase, finally followed by a phase of acute leukemia, which is the blastic phase [42].

Approximately 10 % of cases of this type of leukemia occur in childhood. Characterized by the expansion of hematopoietic stem cells, this is a myeloproliferative disease. CML is associated with the Philadelphia chromosome (Ph), which is the result of a translocation between the long arms of chromosomes 9q34 and 22q11, and the result of this translocation is the hybrid Bcr-abl protein, with increased tyrosine kinase activity. The Bcr-abl protein has the following possible mechanisms in the pathophysiology of CML: activation of mitogenic signaling, apoptosis reduction, and reduction of cell adhesion to the extracellular matrix. The disease is considered to be biphasic or triphasic; one phase is the idle phase (blasts amount to less than 10 %), which is chronic; the other two phases are more aggressive: accelerated (blasts from 10 to 19 %) and blastic (more than 20 % of the leukocytes in peripheral blood are blasts), which is characterized by genomic instability [17].

At present, CML is not curable with drug therapy, and allogeneic bone marrow (family related or not) transplantation is the only curative treatment, to induce molecular remission with the elimination of Bcr-abl [42].

2.4 Acute Myeloid Leukemia (AML)

The term AML encompasses a group of leukemias arising in the lineage of myeloid precursor cells, erythroid cells, megakaryocytes, and monocytes, and AML arises originally from the clonal transformation of hematopoietic precursors,

acquiring chromosomal rearrangements and multiple gene mutations. Mutated cells have advantages in survival and proliferation; also, their differentiation and apoptosis characteristics are changed [43].

Acute myeloid leukemia is responsible for approximately 20 % of acute leukemias in children and adolescents. Most subtypes of AML are characterized by subpopulations of stem cells, like initiating cells, that have an unlimited self-renewal capacity and an organization similar to that of normal hematopoietic cells [101].

The diagnosis is based on a complete hematological count, to show pancytopenia and blast cells; confirmation is made by bone marrow examination. The diagnosis and classification of the type of AML are based on morphological analysis, cytochemical findings, cytogenetics, fluorescence in situ hybridization, immunophenotyping using flow cytometry, and molecular evidence (such as mutation analysis) [56].

In AML is variable, according to the patient, the stage of maturation arrest of granulopoiesis. The cells are the predominant cells that accumulate at some stage in granulopoiesis and provide morphological characteristics, which are used for classification. Analysis of bone marrow and peripheral blood is done with smears; if hypoplastic marrow puncture reveals material with few cells, bone marrow biopsy is needed. Classification after the bone marrow analysis is done according to the French-American-British (FAB) classification (a universal standard). In this classification created by a French-American-British group of morphologists, the diagnosis of AML is given based on the high number of erythroblasts in the bone marrow, associated with a high percentage of myeloid blasts. The FAB classification is based on morphological and cytochemical characteristics; from it the morphological, immunological, and cytogenetic (MIC) of AML classification was created [36].

Table 2.1 Types of acute myeloid leukemia (AML) and characteristics

AML subtype	Differentiation	Clinical and biological specifications
M0	Undifferentiated leukemia	Similar to ALL, requires CD13, CD33, and CD117 and absence of lymphoid markers.
M1	AML without differentiation	Myeloperoxidase + by flow cytometry
M2	Acute myeloid leukemia with differentiation	Auer Rods, common translocation of chromosomes 8 and 21, chloroma. Good prognosis.
M3	Pro-Acute myeloid leukemia	Auer Rods, translocation of chromosomes 15 and 17, disseminated intravascular coagulation. Good prognosis with ATRA.
M4	Myelomonoblastic acute leukemia	Mixed myeloblasts (20 %) and monoblasts, peripheral monocytosis.
M5	Acute monocytic leukemia	Over 80 % of non-erythroid bone marrow cells are monocytes, mixed lineage leukemia with rearrangement of chromosomes 11 and 23 in children. Chloroma.
M6	Erythroleukemia	Rare in children.
M7	Acute megakaryoblastic leukemia	Classical in patients with Down syndrome with mutation of GATA1, good prognosis. Rare in patients without Down syndrome with translocation of chromosomes 1 and 22, in this case bad prognosis.

ALL acute lymphoblastic leukemia, *ATRA* Trans-retinoic acid/tretinoin (not to be confused with isotretinoin)

Source: Based on information from Hastings et al. [26].

2.5 Acute Lymphoblastic Leukemia (ALL)

The clinical manifestation of ALL is the result of direct invasion to the bone marrow, causing cytopenias, such as anemia, leukopenia, and thrombocytopenia; also there is rare extramedullary involvement, such as fever, bleeding, and pain in the bones. Children with ALL usually have non-specific symptoms reported: anemia and fatigue, as well as irritability and anorexia [26].

The mononuclear cells affected are those of lymphoid lineage; approximately 65 % of infant acute leukemias are of B cell precursors, 15 % are T cell precursors, and 20 % of infant acute leukemias are myeloid. ALL can be divided according to the stage where the arrest of cell maturation has occurred: pro-B ALL, ALL-c (common), and pre-B ALL. The divisions are due to phenotypic expressions; thus: pro-B ALL = HLA-DR+/TdT+/CD19+/cCD79+/CD10-; ALL common = HLA-DR+/TdT+/CD19+/CD10+; pre-B ALL = HLA-DR+/TdT+/CD19+/CD10+/CD20+/μ+; ALL-B = HLA-DR+/TdT-/CD19+/CD10+-/CD20+/SmIg+ [18].

Table 2.2 Types of acute lymphoblastic leukemia and hematological characteristics

Type of acute lymphoblastic leukemia French-American-British (FAB)Classification	**Hematological characteristics**
L1	Small and homogeneous blasts, high nucleus/cytoplasm relationship, difficult to observe nucleolus.
L2	Heterogeneous blasts of varying sizes, low nucleus/cytoplasm relationship, nucleoli large and conspicuous.
L3	Large blasts, abundant basophilic and vacuolated cytoplasm. Bad prognosis.

Source: Based on information from Lorenzi [36].

2.6 Osteosarcoma

Osteosarcoma is the most common malignant bone tumor in childhood and adolescence [10, 92]. The prognosis is linked to many variables, such as primary tumor location, initial size, presence of metastasis at diagnosis, histological subtype, and cytogenetic alterations [10]. It is a tumor that often has a poor prognosis and high mortality when it metastasizes [91].

Osteosarcoma is a sarcoma, with the production of osteoid directly from the sarcomatous stroma. Osteosarcoma is a group that can be subdivided, according to the predominant cell type. There can be mixtures of cell types in any given tumor, particularly in the osteoblastic and chondroblastic types. When the predominant extracellular component is osteoid the tumors are categorized as osteoblastic, the most common type of osteosarcoma. Another classification is chondroblastic, with a malignant cartilaginous component. The third classification is fibroblastic—patients have a "herring-bone pattern", similar to that observed in fibrosarcomas. No significant differences in overall outcome are apparent between these three histological subtypes, although patients with fibroblastic histology tend to have better histological responses [92, 93]. Another subgroup is the telangiectatic, which is an unusual variant of osteosarcoma, accounting for 3–10 % of all osteosarcomas; on radiography, these tumors appear as purely lytic destructive lesions located in the metaphyses of long bones [93, 94]. There are other variants, such as small cell osteosarcoma, osteoblastic-like osteosarcomas, giant cell-rich osteosarcomas, and malignant fibrous histiocytoma-like osteosarcomas, but these are much more uncommon [93].

The relationship of osteosarcoma with the peak of puberty suggests a relation between accelerated bone growth and malignant transformation [91]. The entity is very rare in children under 5 years old; the peak incidence occurs at approximately 16 years old for girls and 18 years old for boys [91].

It is a difficult disease to diagnose early because the radiographs may be normal, and signs and symptoms may be nonspecific, so it is important to follow-up children with bone pain without an established diagnosis. The most frequently

seen locations are those with the most bone activity, such as locations close to the growth plate regions, often the femur and the tibia, especially in the knee region [10]. The diagnosis is established from histology [91].

2.7 Central Nervous System (CNS) Tumors

The diagnosis of CNS tumors can be difficult to establish, varying according to the age of the child and the location of the tumor. The symptoms are non-specific and the diagnosis is made from suspicion and the evaluation of symptoms and their duration; infratentorial tumors are often associated with hydrocephalus and 50 % of children with brain tumors have signs of increased intracranial pressure. Headache is present in 70 % of children with posterior fossa tumors and in 50 % of children with central tumor symptoms. The differentiation of headache related to tumor and primary headache syndrome includes nausea and vomiting in the first case, especially in the morning; also, CNS tumors include abnormalities on neurological examination. Symptoms of spinal cord tumors are caused by compression of the spinal cord or nerves enclosed by the tumor mass, and the most common symptom is pain. Intramedullary spinal tumors usually originate from glial cells; the most common histologies are astrocytoma, oligodendroglioma, and myxopapillary ependymoma. Extramedullary tumors are classified as intradural (neurofibroma, schwannoma, meningioma) or extradural (a tumor not originating in the CNS, but a metastatic tumor that originated elsewhere, such as neuroblastoma, Ewing's sarcoma, or lymphoma) [27].

Primitive neuroectodermal tumors are the most common malignant brain tumor in children. They are categorized as medulloblastoma (occurs in the cerebellum), pinealoblastoma (located in the pineal gland), and supratentorial (occurs in the supratentorial region). Gliomas account for over 50 % of CNS tumors in children; this group of tumors includes astrocytomas (60 % of gliomas in children), ependymomas (15 % of gliomas in children), oligodendrogliomas (15 % of gliomas in children), mixed gliomas (5 % of gliomas in children), and other non-specified tumors of glial cells (5 % of gliomas in children) [27].

Table 2.3 Major oncological diseases in children

Diseases	Main diagnostics	Main characteristics
Hodgkin Lymphoma (HL)	Biopsy, lumbar puncture, computed tomography (CT) scan and magnetic resonance image [43]. Differential diagnosis between classic and lymphocytic predominance is done by immunohistochemistry [17].	Giant cells, bi- or multinuclear, called Reed-Sternberg cells (or variants thereof) that characterize 1 % of lymphoma cells in tissues, and the rest consist of inflammatory cells [17].
Non-Hodgkin Lymphoma (NHL)	Biopsy of bone marrow aspirate, lumbar puncture, pleural or peritoneal fluid sampling, immunohistochemistry, flow cytometry [100].	Accounts for 6 % of total childhood cancers, and is frequently high grade. It can be divided into three specific categories: mature B-cell (including Burkitt lymphoma, Burkitt-like lymphoma, and diffuse large B-cell lymphoma); lymphoblastic lymphoma (mostly precursor T-cell); and anaplastic large-cell lymphoma (mature T-cell or null-cell). Currently, the cure rate for childhood NHL is 90 % [99]. Lymphoblastic lymphoma represents approximately 30 % of all pediatric NHL cases and the vast majority are advanced-stage lymphoblastic lymphomas with a precursor T-cell immunophenotype [98].

(continued)

Table 2.3 (continued)

Diseases	Main diagnostics	Main characteristics
Chronic myeloid leukemia (CML)	History and physical examination; complete blood count (CBC) and platelet count; peripheral blood morphology; alkaline phosphatase of the neutrophils in peripheral blood; myelogram; cytochemistry and immunophenotyping (only in blast phase); bone marrow cytogenetics; qualitative polymerase chain reaction (PCR; search for molecular markers); Bcr/abl in peripheral blood or bone marrow; bone marrow biopsy, including determination of medullary fibrosis [42]. Presence of the Philadelphia chromosome (Ph), Bcr-abl hybrid protein with increased tyrosine kinase activity [36]. Differential diagnosis: indolent phase (blasts less than 10 %), accelerated phase (blasts from 10 to 19 %), and blast phase (more than 20 % of the leukocytes in peripheral blood are blasts) [36].	Clonal malignancy disease, excessive proliferation of myeloid lineage [38]. Expansion of hematopoietic stem cells, a myeloproliferative disease. The Bcr-abl protein activates mitogenic signaling, reduces apoptosis, and reduces the adhesion of cells to the extracellular matrix. The blast phase is characterized by genomic instability [36]. It is a curable disease with drug therapy and allogeneic bone marrow transplant (BMT), which is the only curative form of treatment [42].

Acute Myeloid Leukemia (AML)	Analysis of bone marrow and peripheral blood by smears; if hypoplastic marrow puncture reveals material with few cells, bone marrow biopsy is needed. Classification after the bone marrow analysis is done according to the French-American-British (FAB) classification (a universal standard), in which the diagnosis of AML is given based on a high number of erythroblasts in the bone marrow, associated with a high percentage of myeloid blasts. The FAB classification is based on morphological and cytochemical characteristics; from it the morphological, immunological, and cytogenetic (MIC) of AML classification was created [36].	Maturation arrest of granulocytogenesis [36]. Complete blood count (pancytopenia and blast cells), disease confirmed by bone marrow examination. The diagnosis and classification of the type of AML are based on morphological analysis, cytochemistry, cytogenetics, fluorescent in situ hybridization, immunophenotyping using flow cytometry, and molecular evidence (such as mutation analysis) [56].

(continued)

Table 2.3 (continued)

Diseases	Main diagnostics	Main characteristics
Acute Lymphoblastic Leukemia (ALL)	Differential diagnosis: The different types of ALL are due to different phenotypic expressions, thus: pro-B ALL = HLA-DR+/TdT+/CD19+/cCD79+/CD10-; ALL common = HLA-DR+/TdT+/CD19+/CD10+; pre-B ALL = HLA-DR+/TdT+/CD19+/CD10+/CD20+/μ+; ALL-B = HLA-DR+/TdT-/CD19+/CD10+-/CD20+/SmIg + [18].	The clinical manifestation of ALL is the result of direct invasion to the bone marrow, causing cytopenias, such as anemia, leukopenia, and thrombocytopenia. Also, there is rare extramedullary involvement, such as fever, bleeding, and pain in the bones. Children with ALL often have non-specific symptoms, reported as anemia, fatigue, irritability and anorexia [26].
Osteosarcoma	Complete blood cell counts. Levels of alkaline phosphatase and lactate dehydrogenase, which must be high and are associated with osteosarcoma. Imaging studies with plain radiographs. Osteosarcoma commonly produces dense sclerosis in the metaphyses of the long bones, extending to soft tissues. Also common are radial calcifications and sclerotic bone lesions. Bone tumors in which there is a suspicion of malignancy should be biopsied [28].	Osteosarcoma is the most common malignant bone tumor in childhood and adolescence [10, 92]. The prognosis is linked to many variables, such as primary tumor site, initial size, presence of metastasis at diagnosis, histological subtype, and cytogenetic alterations. The initial diagnosis is difficult; radiographs may be normal and the signs and symptoms may be non-specific. The most common sites involved are those with the highest bone activity, such as sites close to the growth plate regions, often the femur and the tibia, especially in the knee region [10]. It is a tumor that often has poor prognosis and high mortality when it metastasizes [91].

Central Nervous System (CNS) Tumors	Imaging studies, magnetic resonance imaging, positron emission tomography (PET), computed tomography (CT; single-photon emission). Lumbar puncture to check for metastasis in the arachnoid space. Bone scan to look for extraneural metastasis in patients with medulloblastoma (90 % of metastasis is to the bones). Infratentorial tumors are associated with hydrocephalus, and 50 % of children with brain tumors have intracranial hypertension. Headache is present in 70 % of children with posterior fossa tumors and in 50 % of children with central tumor symptoms. The differentiation of headache related to tumor and primary headache syndrome includes nausea and vomiting in the first case, especially in the morning, the differentiation also includes abnormalities on the neurological examination. Symptoms of spinal cord tumors are caused by compression of the spinal cord or nerves encased by tumor; most commonly the symptom is back pain [25].	Intramedullary spinal tumors usually originate from glial cells; the most common histologies are astrocytoma, oligodendroglioma, and myxopapillary ependymoma. Extramedullary tumors are classified as intradural (neurofibroma, schwannoma, meningioma) or extradural (a tumor originating not in the CNS, but a metastatic tumor that originated elsewhere, such as neuroblastoma, Ewing's sarcoma, or lymphoma) [25]. Primitive neuroectodermal tumor is the most common malignant brain tumor in children. It is categorized as medulloblastoma (occurs in the cerebellum), pinealoblastoma (located in the pineal gland), and supratentorial (occurs in the supratentorial region). Gliomas account for over 50 % of CNS tumors in children; this group of tumors includes astrocytomas (60 % of gliomas in children), ependymomas (15 % of gliomas in children), oligodendrogliomas (15 % of gliomas in children) mixed gliomas (5 % of gliomas in children), and other non-specified tumors of glial cells (5 % of gliomas in children) [27].

Chapter 3
The Main Protocols in Pediatric Oncohematology

The protocols cited here are for quick reference, not dispensing the full study of each protocol before prescribing. Protocols may vary according to each institution.

List of tables

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Drug Therapy and Interactions in Pediatric Oncology,
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3.1 Hodgkin Lymphoma

For the treatment of Hodgkin lymphoma in children, one of the most commonly used protocols in pediatrics is the ABVD protocol (doxorubicin, bleomycin, vinblastine, and dacarbazine, on days 1 and 15, repeating the cycle every 28 days); opinion on this protocol for children is not unanimous as it is in adults, due to the cardiotoxicity of anthracyclines and the risk of pulmonary fibrosis due to bleomycin [11, 17, 103].

Advances made in the treatment of Hodgkin lymphoma mean that most patients with this diagnosis are cured or that the disease can be controlled for years. Therefore, reduction of the long-term toxicity of the chemotherapy and the maintenance of a good quality of life are the major issues in the present pharmacological treatment of this disease [97].

Table 3.1 Protocol ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine)

Drug	Administration	Dose	Days (D)
Doxorubicin	IV	25 mg/m²/day	D1 and 15
Bleomycin	IV	10 IU/m²/day	D1 and 15
Vinblastine	IV	6 mg/m²/day	D1 and 15
Dacarbazine	IV	375 mg/m²/day	D1 and 15

Source: Based on information from Chu and the National Cancer Institute [11, 85]
IU International units

Table 3.2 Protocol COPP (cyclophosphamide, vincristine, procarbazine, and prednisone)

Drug	Administration	Dose	Days
Cyclophosphamide	IV	600 mg/m²/day	D1 and 8
Vincristine	IV	1.4 mg/m²/day (maximum dose per day is 2 mg)	D1 and 8
Procarbazine	Oral	100 mg/m²/day	D1 to D15
Prednisone	Oral	40 mg/m²/day	D1 to D15

Source: Based on information from the National Cancer Institute [85]

Table 3.3 Protocol COPDAC (cyclophosphamide, vincristine, dacarbazine, and prednisone)

Drug	Administration	Dose	Days
Cyclophosphamide	IV	600 mg/m²/day	D1 and 8
Vincristine	IV	1.4 mg/m²/day (maximum dose per day is 2 mg)	D1 and 8
Dacarbazine	IV	250 mg/m²/day	D1 to D3
Prednisone	Oral	40 mg/m²/day	D1 to D15

Source: Based on information from the National Cancer Institute [85]

Table 3.4 Protocol OPPA (doxorubicin, vincristine, procarbazine, and prednisone)

Drug	Administration	Dose	Days
Doxorubicin	IV	40 mg/m²/day	D1 and 15
Vincristine	IV	1.5 mg/m²/day (maximum dose per day is 2 mg)	D1, 8 and 15
Procarbazine	Oral	100 mg/m²/day	D1 to D15
Prednisone	Oral	60 mg/m²/day	D1 to D15

Source: Based on information from the National Cancer Institute [85]

Table 3.5 Protocol OEPA (doxorubicin, vincristine, etoposide, and prednisone)

Drug	Administration	Dose	Days
Doxorubicin	IV	40 mg/m²/day	D1 and 15
Vincristine	IV	1.5 mg/m²/day (maximum dose per day is 2 mg)	D1, 8 and 15
Etoposide	IV	125 mg/m²/day	D3 to 6
Prednisone	Oral	60 mg/m²/day	D1 to D15

Source: Based on information from the National Cancer Institute [85]

Table 3.6 Protocol COPP/ABV (cyclophosphamide, vincristine, procarbazine and prednisone/doxorubicin, bleomycin and vinblastine)

Drug	Administration	Dose	Days
Cyclophosphamide	IV	600 mg/m²/day	D0
Vincristine	IV	1.4 mg/m²/day (maximum dose per day is 2 mg)	D0
Procarbazine	Oral	100 mg/m²/day	D0 to D6
Prednisone	Oral	40 mg/m²/day	D0 to D13
Doxorubicin	IV	35 mg/m²/day	D7
Bleomycin	IV	10 IU/m²/day	D7
Vinblastine	IV	6 mg/m²/day	D7

Source: Based on information from the National Cancer Institute [85]

Table 3.7 Protocol VAMP (vinblastine, doxorubicin, methotrexate [MTX], and prednisone)

Drug	Administration	Dose	Days
Vinblastine	IV	6 mg/m²/day	D1 and 15
Doxorubicin	IV	25 mg/m²/day	D1 and 15
Methotrexate	IV	20 mg/m²/day	D1 and 15
Prednisone	Oral	40 mg/m²/day	D1 to D14

Source: Based on information from the National Cancer Institute [85]

Table 3.8 Protocol DBVE (doxorubicin, bleomycin, vincristine, and etoposide)

Drug	Administration	Dose	Days
Doxorubicin	IV	25 mg/m²/day	D1 and 15
Bleomycin	IV	10 IU/m²/day	D1 and 15
Vincristine	IV	1.5 mg/m²/day (maximum dose per day is 2 mg)	D1 and 15
Etoposide	IV	100 mg/m²/day	D1 to D5

Source: Based on information from the National Cancer Institute [85]

Table 3.9 Protocol ABVE-PC (doxorubicin, bleomycin, vincristine and etoposide – prednisone and cyclophosphamide)

Drug	Administration	Dose	Days
Doxorubicin	IV	30 mg/m²/day	D0 and D1
Bleomycin	IV	10 IU/m²/day	D0 and D7
Vincristine	IV	1.4 mg/m²/day (maximum dose per day is 2 mg)	D0 and D7
Etoposide	IV	75 mg/m²/day	D0 to D4
Prednisone	Oral	40 mg/m²/day	D0 to D9
Cyclophosphamide	IV	800 mg/m²/day	D0

Source: Based on information from the National Cancer Institute [85]

Table 3.10 Protocol BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and procarbazine)

Drug	Administration	Dose	Days
Bleomycin	IV	10 IU/m²/day	D7
Etoposide	IV	200 mg/m²/day	D0 to D2
Doxorubicin	IV	35 mg/m²/day	D0
Cyclophosphamide	IV	1200 mg/m²/day	D1 and D8
Vincristine	IV	2 mg/m²/day (maximum dose per day is 2 mg)	D7
Prednisone	Oral	40 mg/m²/day	D0 to D13
Procarbazine	Oral	100 mg/m²/day	D0 to D6

Source: Based on information from the National Cancer Institute [85]

Table 3.11 Protocol CVP (cyclophosphamide, vinblastine, and prednisolone)

Drug	Administration	Dose	Days
Cyclophosphamide	IV	500 mg/m²/day	D1
Vinblastine	IV	6 mg/m²/day	D1 and 8
Prednisolone	Oral	40 mg/m²/day	D1 to D8

Source: Based on information from the National Cancer Institute [85]

3.2 Chronic Myeloid Leukemia (CML)

The first-line treatment is done with imatinib; can consider referring the patient for an allogeneic transplantation if he/she have a compatible bone marrow donor. The treatment of CML in the chronic phase, after the failure of imatinib, consists of autologous transplantation. Treatment of CML in the accelerated phase is done with allogeneic transplantation; imatinib can be used before. In CML in blast crisis, treatment is done with imatinib following an allogeneic transplantation, but only if the patient shows response to the treatment,

including return to the chronic phase. The experience with imatinib in children, although limited, has shown cytogenetic responses similar to those in adult patients [17].

3.2.1 Hematological Control with Hydroxyurea

Table 3.12 CML hematological control with hydroxyurea – variation I (of INCA – Brazilian National Institute of Cancer)

Drug	Administration	Dose
Hydroxyurea	Oral	50 mg/kg/day in children with weight <30 kg 2 g/m^2/day in children with weight >30 kg
Hydroxyurea – Maintenance	Oral	10 to 30 mg/kg/day

Source: Based on information from the Brazilian Ministry Of Health [42]

Maintenance is interrupted if the number of leukocytes falls below 2500/mm^3 and platelets fall to below 100,000/mm^3, returning to maintenance when the values normalize.

A hematological response corresponds to a 50 % reduction of the initial leukocyte count, maintained for at least 2 weeks. Complete hematological response is considered as a leukocyte count below 10,000/mm^3, the absence of promyelocytes or myeloblasts, less than 5 % myelocytes or metamyelocytes, and about 450,000 platelets/mm^3, maintaining the above conditions for at least 4 weeks.

Cytogenetic response may be absent if the number of Philadelphia (Ph) chromosome-positive cells is greater than 90 %; response is considered to belower if 35–90 % of the cells are Ph chromosome-positive; partial, if there are 5–34 % of Ph chromosome-positive cells; complete if 0% of Ph chromosome-positive cells; or greater, which corresponds to the sum of full and partial responses (less than 35 % of Ph chromosome-positive cells) [42].

Table 3.13 CML hematological control with hydroxyurea – variation II

Drug	Administration	Dose
Hydroxyurea	Oral	30–40 mg/kg/day or 0.5–1 g/m^2/day. To be adjusted according to reduction of white blood cell count.

Source: Based on information from Lee [86]

Hydroxyurea should be discontinued when the white blood cell levels are around 20,000–10,000/mm^3. Hydroxyurea can lead to complete hematological response in some cases, but there is an unusual cytogenetic response (in 0–5 % of the cases), in which it has no impact on the prevention of disease progression, or on the substantial prolongation of survival [66, 86].

3.2.2 Imatinib

Imatinib dose ranges of up to 800 mg/day, divided into two doses of 400 mg, are included in the U.S.A. National Comprehensive Cancer Network (NCCN) CML guidelines, if tolerated, for disease progression, lack of hematological response after 3 months, lack of cytogenetic response after 6–12 months, or loss of previous hematological or cytogenetic response [59].

Table 3.14 Imatinib for CML chronic phase, newly diagnosed, Ph+

Drug	Administration	Dose
Imatinib	Oral	340 mg/m^2/day once a day or divided into two doses. Maximum dose is 600 mg per day.

Source: Based on information from Taketomo et al. [59]

Table 3.15 Imatinib for CML chronic phase, Ph+

Drug	Administration	Dose
Imatinib	Oral	400 mg once a day, may be increased to 600 mg per day.

Source: Based on information from Taketomo et al. [59]

Table 3.16 Imatinib for CML accelerated phase or blast crisis, Ph+

Drug	Administration	Dose
Imatinib	Oral	600 mg once a day

Source: Based on information from Taketomo et al. [59]

If tolerated, the imatinib dose may be increased to 800 mg per day, divided into two doses of 400 mg, for disease progression, lack of hematological response after 3 months, lack of cytogenetic response after 6–12 months, or loss of previous hematological or cytogenetic response [59].

3.3 Acute Myeloid Leukemia (AML)

Despite the lack of targeted therapy for most subtypes, and few new agents to treat AML, survival rates have reached as high as 60 % for children treated in developed countries, but cure rates for some subtypes of childhood AML remain very low, and novel therapies are needed [101].

The pharmacological treatment in general is divided into two phases: A remission induction and a post-induction treatment [36].

3.3.1 Protocol of the German Group for Acute Myeloid Leukemia Treatment Berlin-Frankfurt-Münster (BFM2004): Adapted from HEMORIO

The child protocol is used until age 16 years; later, the adult protocol 7 + 3 is used, as per the standardization of HEMORIO [29].

Patients should be divided into two risk groups:

- Standard Risk [29]

  M3, AML in patients with Down syndrome, M1 or M2 with Auer rods, eosinophilic M4, AML with translocation of chromosomes (8; 21)/inversion (16).

- High Risk [29]

  M0, M1/M2 without Auer rods, M4, M5, M6, and M7. If bone marrow on D15 > 5% of blasts, patient will be high-risk.

Patients with indication for stem cell transplantation are: all high-risk patients in first remission with related bone marrow donors; unrelated donors can be considered for high-risk patients with prolonged aplasia (more than 4 weeks after HAM protocol) without signs of spinal cord regeneration.

Table 3.17 Cytoreductive phase for acute myeloid leukemia in the 2004 Protocol of the German Leukemia Treatment Group (BFM2004): For patients with initial leukocyte count greater than 50,000/mm^3 or large visceromegalies

Drug	Administration	Dose
Thioguanine	Oral	40 mg/m^2/day
Cytarabine	IV or SUB-Q	40 mg/m^2/day

Source: Based on information from Hemorio [29]
SUB-Q Subcutaneous

The cytoreductive phase should not exceed 7 days, if no significant reduction in leukocyte counts on D3, start the induction.

Table 3.18 Induction phase of acute myeloid leukemia protocol of 2004 of the German Leukemia Treatment Group (BFM2004)

Drug	Administration	Dose	Days
Cytarabine	IV in 48 h	100 mg/m^2/day	D1 and 2
Cytarabine	IV	100 mg/m^2/dose 12/12 h	D3 to 8
Idarubicin	IV in 4 h (Before Ara-C)	12 mg/m^2	D3, 5, and 7
Etoposide	IV in 1 h (6 h before Ara-C)	150 mg/m^2	D6, 7, and 8
Cytarabine	IT	Dose according to age	D1 and 8

Source: Based on information from Hemorio [29]
Ara-C Cytarabine

Table 3.19 Dose of intrathecal cytarabine in induction phase of acute myeloid leukemia protocol of 2004 of the German Leukemia Treatment Group (BFM 2004)

Age	Dose of intrathecal cytarabine
<1 year old	20 mg
1–2 years old	26 mg
2–3 years old	34 mg
3 years old or older	40 mg

Source: Based on information from Hemorio [29]

Table 3.20 Examination of bone marrow induction phase of acute myeloid leukemia protocol of 2004 of the German Leukemia Treatment Group (BFM2004): To do the bone marrow examination on D15 of the induction phase

Blasts on D15	Continue the Protocol
<5 % or equal	D 28 if afebrile and in good general condition
>5 %	D16 if there is no fever or severe infection

Source: Based on information from Hemorio [29]

- Second induction (HAM – High-dose cytarabine and mitoxantrone of second induction – Do not confuse with haM of second consolidation)

Only the high-risk group. Patients should have good general condition and leukocytes >1000/m^3 on D15 to start the next block. If patient presents blasts on D15, he should receive the next block, even with fewer leukocytes, if the patient's condition permits. Bone marrow puncture on D1.

Table 3.21 Second induction for acute myeloid leukemia of the 2004 protocol of the German Leukemia Treatment Group (BFM2004)

Drug	Administration	Dose	Days
Cytarabine (high dose)	IV in 3 h	3 g/m^2 every 12 h	D1 to 3 (six doses)
Mitoxantrone	IV in 30 min	10 mg/m^2	D3 and 4
Cytarabine	IT	Dose according to age	D1 (with an interval of at least 2 h between the first Ara-C IV and IT dose)

Source: Based on information from Hemorio [29]
IT intrathecal

Table 3.22 Dose of intrathecal cytarabine – second induction phase for acute myeloid leukemia 2004 protocol of the German Leukemia Treatment Group (BFM2004)

Age	Dose of intrathecal cytarabine
<1 year old	20 mg
1–2 years	26 mg
2–3 years	34 mg
3 years old or older	40 mg

Source: Based on information from Hemorio [29]

Table 3.23 Adjustment of cytarabine EV dose of the 2004 protocol of the German Leukemia Treatment Group (BFM2004): according to age

Age (in months)	% of dose to be given
≥24	100
20 to 24	90
17 to 19	80
14 to 16	70
11 to 13	60
8 to 10	50
6 to 7	40
4 to 5	30
≤3	20

Source: Based on information from Hemorio [29]

Supportive care: lubricant eye drops every 4–6 h, starting 6 h prior to first dose of cytarabine and ending 12 h after the last dose.

- Consolidation Phase – Part I (AI)

This phase begins 4 months after the induction in each group. The patient needs to have good general condition, absence of infection, polymorphonuclear neutrophil (PMN) count >1000/mm^3, platelets >80,000/mm^3.

Marrow puncture on D1.

Table 3.24 Consolidation phase for acute myeloid leukemia in the 2004 protocol of the German Leukemia Treatment Group (BFM2004) – part I (AI)

Drug	Administration	Dose	Days
Cytarabine	IV in continuous infusion	500 mg/m^2	D1 to 4
Idarubicina	IV in 60 min	7 mg/m^2	D3 and 5
Cytarabine	IT	Dose according to age	D1 and 6

Source: Based on information from Hemorio [29]

Table 3.25 Dose of intrathecal cytarabine – consolidation phase for acute myeloid leukemia in the 2004 protocol of the German Leukemia Treatment Group (BFM2004) – part I (AI)

Age	Dose of intrathecal cytarabine
<1 year old	20 mg
1–2 years old	26 mg
2–3 years old	34 mg
3 years old or older	40 mg

Source: Based on information from Hemorio [29]

- Consolidation Phase (haM: high-dose cytarabine and mitoxantrone of second consolidation – Do not confuse with HAM of second induction) – Part Two

Starting 4 weeks after the part I, it is necessary that the patient is in good general condition, with no infections, PMN >1000/mm^3 and platelets >80,000/mm^3.

Table 3.26 Consolidation phase for acute myeloid leukemia of the 2004 protocol of the German Leukemia Treatment Group (BFM2004) – part two (haM)

Drug	Administration	Dose	Days
Cytarabine (high dose)	IV in 3 h	1 g/m^2 12 in 12 h	D1 to 3 (six doses)
Mitoxantrone	IV in 30 minutes	10 mg/m^2	D3 and 4
Cytarabine	IT	Dose according to age	D1 and 6

Source: Based on information from Hemorio [29]

Table 3.27 Dose of intrathecal cytarabine – consolidation phase for acute myeloid leukemia of the German Leukemia Treatment Group (BFM2004) – part two (haM)

Age	Dose of intrathecal cytarabine
<1 year old	20 mg
1–2 years old	26 mg
2–3 years old	34 mg
3 years old or older	40 mg

Source: Based on information from Hemorio [29]

Observe the precautions for use of cytarabine (dose adjustment, lubricant eye drops).

- Intensification phase (HAE – High-dose cytarabine and etoposide of intensification phase)

  For all patients without predicted transplantation.

  Start 2–4 weeks after haM, the patient must have good general condition, absence of infections, PMN >1000/mm^3, and platelets >80,000/mm^3. Bone marrow puncture on D1.

Table 3.28 Intensification phase (HAE) for acute myeloid leukemia of the 2004 protocol of the German Leukemia Treatment Group (BFM2004)

Drug	Administration	Dose	Days
Cytarabine (high dose)	IV in 3 h	3 g/m^2 12 in 12 hours	D1 to 3 (six doses)
Etoposideo	IV in 60 minutes	125 mg/m^2	D2 to 5 (6 h before Ara-C)
Cytarabine	IT	Dose according to age	D1

Source: Based on information from Hemorio [29]

Table 3.29 Dose of intrathecal cytarabine – enhancement phase for acute myeloid leukemia – of the German Leukemia Treatment Group (BFM2004)

Age	Dose of intrathecal cytarabine
<1 year old	20 mg
1–2 years old	26 mg
2–3 years old	34 mg
3 years old or older	40 mg

Source: Based on information from Hemorio [29]

Observe the precautions in relation to Ara-C (dose adjustment, eye drops).

- Maintenance Phase (duration 1 year)

Beginning 4 weeks after the end of the final of the intensification, parallel radiotherapy, provided that the general condition and hematological findings permit.

Table 3.30 Maintenance phase for acute myeloid leukemia of the German Leukemia Treatment Group (BFM2004)

Drug	Administration	Dose	Days
Cytarabine	Sub-Q	40 mg/m^2	D1 to 4 (every 4 weeks)
Thioguanine	Oral	40 mg/m^2	Daily
Cytarabine	IT	Dose according to age	D1, 8, 15, and 22

Source: Based on information from Hemorio [29]

Table 3.31 Dose of intrathecal cytarabine – maintenance phase for acute myeloid leukemia – of the German Leukemia Treatment Group (BFM2004)

Age	Dose of intrathecal cytarabine
<1 year old	20 mg
1–2 years old	26 mg
2–3 years old	34 mg
3 years old or older	40 mg

Source: Based on information from Hemorio [29]

Table 3.32 Adjusting the dose of thioguanine according to the German Leukemia Treatment Group (BFM2004): according to leukocyte count

White blood cell count (in mm^3)	Percentage of thioguanine to be administered
>3000	150 %
>2000	100 %
1000–2000	50 %
<1000	0 %

Source: Based on information from Hemorio [29]

Cytarabine should be given if the leukocyte count result is >2000/mm^3 and platelets >80,000/mm^3; if the results are lower, postpone for a week.

- Children with AML and Down syndrome: Keep the protocol, with the following changes:

Reduce Ara-C dose according to reduction indicated for patients less than 2 years old, during induction (AIE – Ara-C, idarrubicina and etoposide) reduce the dose of idarubicin to 8 mg/m^2; these patients should not receive the HAM (second induction) block of the protocol; idarubicin in the AI block to be reduced to 5 mg/m^2 and mitoxantrone in the haM block (second consolidation) should be reduced to 7 mg/m^2; treatment of the CNS must be restricted to seven doses of Ara-C IT.

- Children with AML M3:

These children should be treated as a standard-risk group, regardless of the number of blasts on D15 of induction, followed by chemotherapy as the clinical condition allows.

Patients with a positive molecular marker after the HAE block should receive ATRA (trans retinoic acid or tretinoin; not to be confused with isotretinoin) to the negative of molecular marker, then go to the HAM block (of second induction).

Table 3.33 Tretinoin in children with acute myeloid leukemia M3; 2004 protocol of the German Leukemia Treatment Group (BFM2004)

Drug	Administration	Dose	Period
ATRA	Oral, with meal	25 mg/m^2/day (to divide this dose in two doses a day)	Start immediately after confirmation of the diagnosis, do 3 days before starting the chemotherapy protocol.

Source: Based on information from Hemorio [29]
ATRA trans retinoic acid, same as tretinoin. Not to be confused with isotretinoin

Administer intermittently for 14 days, with 7 days of rest. In general, complete remission is achieved after the third cycle of ATRA. After that, ATRA will be administred again at the beginning of the HAE cycle for 14 days. Then, it will be administred 3 months after the sart of maintenance, for 14 days, every 3 months.

Table 3.34 Start of chemotherapy in children with acute myeloid leukemia M3, the 2004 protocol of the German Leukemia Treatment Group (BFM2004)

If initial white blood cell count <5000/mm^3	Start chemotherapy after the 3rd day of ATRA
If initial white blood cell count >5000/mm^3	Start chemotherapy after the 1st day of ATRA
If initial white blood cell count >10,000/mm^3	Start chemotherapy simultaneously with ATRA

Source: Based on information from Hemorio [29]

ATRA syndrome: This syndrome may occur usually 2–10 days after treatment; it is reversible with the temporary suspension of ATRA and treatment with dexamethasone 0.5–2 mg/kg. The ATRA syndrome is characterized by fever, pulmonary infiltrates, pleural or pericardial effusion, and renal failure.

Relapse: Perform FLAG protocol as induction, follow with second induction using the same protocol, followed by consolidation with the same protocol, or allogeneic stem cell transplantation [29].

3.3.2 IDA-FLAG Protocol (Idarubicin, Fludarabine, Cytarabine, and Filgrastim)

Table 3.35 Protocol IDA-FLAG (idarubicin, fludarabine, cytarabine, and filgrastim)

Drug	Administration	Dose	Days
Fludarabine	IV in 30 min	30 mg/m^2/day	D1 to 4
Idarubicin	IV in 1 h. To start 1 h prior to cytarabine.	12 mg/m^2/day	D2 to 4
Cytarabine	IV in 3 h. To start 4 h after the beginning of fludarabine	2000 mg/m^2/day	D1 to 4
Filgrastim	SC	400 μg/m^2	D0 to the day of absolute neutrophil count of $>1.0\times10^9$/L.

Source: Based on information from Fleischhack et al. [87]

The FLAG course is a combined chemotherapy of fludarabine, cytarabine, and filgrastim, as in the IDA-FLAG regimen, but without idarubicin [87].

3.4 Acute Lymphoid Leukemia (ALL)

The pharmacological therapy for ALL is divided into three phases: induction, consolidation, and maintenance. The induction phase is the therapy used until complete remission of disease, which is a prerequisite for long-term survival. The treatment phases of consolidation and maintenance serve to maintain the complete remission and are summarized under the term 'post-remission therapy'; during the period of consolidation therapy, blood stem cell transplantation is performed [102].

3.4.1 Protocol of Leukemia Treatment of the German Group Berlin – Frankfurt – Münsten, of 1995, for Acute Lymphoid Leukemia (BFM95)

Low-risk (in this protocol, same as standard): 1 to less than 6 years old, leukocyte count < 20,000/mm^3 in diagnosis date, absence of T lymphocyte, blasts number in peripheral blood < 1000/mm^3 on D8), no translocation t (9; 22) nor t (4; 11), and complete remission of bone marrow on D33. All these criteria must be fullfilled [7].

Medium-risk: Number of blasts in the peripheral blood < 1000/mm^3 on D8, enter in complete remission on D33, absence of translocation t (9; 22) and t (4; 11), < 1 year or ≥ six years, leukocyte count > 20,000/mm^3 at diagnosis, and presence of T lymphocytes. All these criteria must be fulfilled [7].

High-risk: Number of blasts > 1000/mm^3 in the peripheral blood on D8, without complete remission on D33, with translocations t (9; 22) or t (4; 11). Having at least one of these criteria, the patient is considered high risk [7].

Table 3.36 Induction – phase I protocol I, of the 1995 protocol of the German Leukemia Treatment Group (BFM95) for acute lymphoid leukemia

Drug	Administration	Dose	Days
Prednisone	Oral	60 mg/m²/day	D1 to D28
Vincristine	IV	1.5 mg/m²/day (maximum dose of vincristine = 2 mg/day)	D8, D15, D22, D29
Daunorubicin	IV	30 mg/m²/day	D8, D15, D22, D29 (If low-risk, suspend D22 and 29)
L-Asparaginase	IM, IV	5000 IU/m²/day	D12, D15, D18, D21, D24, D27, D30, D33 If high-risk, suspend D30 and D33
Methotrexate	IT	<1 year old: 6 mg/4 mL NaCl 0.9 % 1–2 years old: 8 mg/6 mL NaCl 0.9 % 2–3 years old: 10 mg/8 mL NaCl 0.9 % >3 years old: 12 mg/10 mL NaCl 0.9 %	D1, D12, D33. If CNS 2 or 3, give in addition on D18 and 27*

Source: Based on information from Möricke et al. [117] and Busato et al. [7]
*In some institucional BFM 95 protocols, MTX IT, in phase I of protocol I, in addition of D1, 12 and 18, is given on D27 and 33 for all risk groups if CNS 2 or 3. In others, is given, in addtion, on days 27 and 33 for standard-risk and medium-risk CNS 2 or 3 patients, and with only additional D18 for high-risk CNS 2 or 3 patients.

If, in the blood count on D8 and bone marrow examination on D33, the patient presents blasts >1000/m³ and >5 % of blasts, respectively, he has to be moved to the high-risk protocol (HR). If the patient still has a low or medium risk, he must be referred to the phase II, in which the patient must have <5 % blasts in bone marrow examination on D33 and complete remission of the CNS disease, > 2000/mm³ leukocytes, > 500/mm³ granulocytes, platelet count > 50,000/mm³, and a 30 % reduction of the mediastinal tumor.

Table 3.37 Phase II/protocol I (only for low and medium-risk patients) of the 1995 protocol of the German Leukemia Treatment Group (BFM95) for acute lymphoid leukemia

Drug	Administration	Dose	Days
Cyclophosphamide	IV	1000 mg/m²/day	D36, D64
Mesna (for cystitis prophylaxis)	IV	400 mg/m²/dose	Hours 0, 4, and 8 from initiation of cyclophosphamide. Use this mesna scheme every day of cyclophosphamide.
Cytarabine	IV or SC	75 mg/m²/day	D38 to D41, D45 to D48, D52 a D55, D59 to D62
Mercaptopurine	Oral	60 mg/m²/day	D36 to D63
Methotrexate	IT	<1 year old: 6 mg/4 mL NaCl 0.9 % 1–2 years old: 8 mg/6 mL NaCl 0.9 % 2–3 years old: 10 mg/8 mL NaCl 0.9 % >3 years old: 12 mg/10 mL NaCl 0.9 %	D45 and D59

Source: Based on information from Möricke et al. [117] and Busato et al. [7]

Should be done a two week pause between phase II of protocol I and maintenance.

Table 3.38 Maintenance phase (M) of the 1995 protocol of the German Leukemia Treatment Group (BFM95) for acute lymphoid leukemia – It is an extracompartment therapy (only for low and medium-risk patients)

Drug	Administration	Dose	Days
Mercaptopurine	Oral	25 mg/m^2/day	D1 to D56
Methotrexate	IV. Administer 1/10 of methotrexate dose in 30 min and the remaining amount in 23 h and 30 min.	5000 mg/m^2/day	D8, D22, D36, D50
Rescue with Leucovorin	First IV, then oral.	Initial dose: 30 mg/m^2/dose; afterward, give five doses every 3 h, at 15 mg/m^2/dose. Then 15 mg/m^2/dose orally every 6 h until the serum level is$<5 \times 10^{-8}$M .	Use this scheme after every MTX IV, first dose is 36 h after the initiation of MTX.
Methotrexate	IT	<1 year old: 6 mg/4 mL NaCl 0.9 % 1–2 years old: 8 mg/6 mL NaCl 0.9 % 2–3 years old: 10 mg/8 mL NaCl 0.9 % >3 years old: 12 mg/10 mL NaCl 0.9 %	D8, D22, D36, D50
Cytarabine (only for medium-risk patients randomized into MR-2)	IV in 24 h	200 mg/m^2/day	D9, D23, D37, D51

Source: Based on information from Möricke et al. [117] and Busato et al. [7]

Table 3.39 Reinduction phase: protocol II/phase I of the 1995 protocol of the German Leukemia Treatment Group (BFM95) for acute lymphoid leukemia

Drug	Administration	Dose	Days
Dexamethasone	Oral	10 mg/m²/day	D1 to D21
Vincristine	IV	1.5 mg/m²/day (maximum dose of vincristine is 2 mg/day)	D8, D15, D22, D29
Doxorubicin	IV	30 mg/m²/day	D8, D15, D22, D29
L-Asparaginase	IM, IV	10,000 IU/m²/day	D8, D12, D15, D18
Methotrexate	IT	<1 year old: 6 mg/4 mL NaCl 0.9 % 1–2 years old: 8 mg/6 mL NaCl 0.9 % 2–3 years old: 10 mg/8 mL NaCl 0.9 % >3 years old: 12 mg/10 mL NaCl 0.9 %	D1 to D28

Source: Based on information from Möricke et al. [117] and Busato et al. [7]

High-risk patients should start the reinduction only after high-risk therapy (Tables 3.41–3.43). Low and medium-risk patients should start the reinduction after phase M (first maintenance – Table 3.38).

Table 3.40 Reinduction phase: protocol II/phase II of the 1995 protocol of the German Leukemia Treatment Group (BFM95) for acute lymphoid leukemia

Drug	Administration	Dose	Days
Cyclophosfamide	IV	1000 mg/m²/day	D36
Mesna (for cystitis prophylaxis)	IV	400 mg/m²/dose	Hours 0, 4, and 8 after initiation of cyclophosphamide.
Mercaptopurine	Oral	60 mg/m²/day	D36 to D49
Cytarabine	SC	75 mg/m²/day	D38 to D41, D45 to D48
Methotrexate	IT	<1 year old: 6 mg/4 mL NaCl 0.9 % 1–2 years old: 8 mg/6 mL NaCl 0.9 % 2–3 years old: 10 mg/8 mL NaCl 0.9 % >3 years old: 12 mg/10 mL NaCl 0.9 %	D38 and D45

Source: Based on information from Möricke et al. [117] and Busato et al. [7]

Reinduction phases I and II of Protocol II, as recommended by the BFM95 protocol, are indicated for ALL in all risk categories; reinduction is also done for the high-risk group (HR); however, this group starts reinduction after high-risk therapy (Tables 3.41–3.43).

Should be done a two week pause between phase II of reinduction and start of maintenance (Tables 3.44 and 3.45).

Table 3.41 Therapy I for high-risk patients (HR-I) of the 1995 protocol of the German Leukemia Treatment Group for acute lymphoid leukemia (BFM95)

Drug	Administration	Dose	Days
Dexamethasone	IV	20 mg/m^2/day (to divide in doses given every 12 h)	D1 to D5
Vincristine	IV	1.5 mg/m^2/day (maximum dose of vincristine is 2 mg/day)	D1, D6
Methotrexate	IV in 24 h (1/10 of dose in 30 min and the remaining amount in 23 h and 30 min.)	5000 mg/m^2/dia	D1
Rescue with Leucovorin	First IV, then oral.	Initial dose: 30 mg/m^2/dose; afterward, give five doses every 3 h, at 15 mg/m^2/dose. Then 15 mg/m^2/dose orally every 6 h until the serum level is $<5 \times 10^{-8}$M	First dose is 36 h after the initiation of MTX.
Cyclophosfamide	IV in 1 h	200 mg/m^2/dose Give every 12 h on D2 and D3, on D4 give just one dose	D2, D3, D4 (Total of five doses)

(continued)

Table 3.41 (continued)

Drug	Administration	Dose	Days
Mesna (for cystitis prophylaxis)	IV	80 mg/m²/dose	Hours 0, 4, and 8 after initiation of cyclophosphamide. Use this scheme every day of cyclophosphamide treatment.
Cytarabine	IV in 3 h	2000 mg/m²/dose every 12 h	D5 (total of 2 doses)
L-Asparaginase	IV in 6 h	25,000 IU/m²/day	D6
MADIT	IT	Up to 1 year old: 6 mg of methotrexate, 16 mg of cytarabine, 2 mg/m² of dexamethasone. 1–2 years old: 8 mg of MTX, 20 mg of Ara-C, 2 mg/m² of DEXA. 2–3 years old: 10 mg of MTX, 26 mg of Ara-C, 2 mg/m² of DEXA. >3 years old: 12 mg of MTX, 30 mg of Ara-C, 2 mg/m² of DEXA.	D1

Source: Based on information from Möricke et al. [117] and Busato et al. [7]
MADIT methotrexate, cytarabine and dexamethasone, all intrathecal
Each HR protocol, in the study, was given twice [117].

Table 3.42 Therapy II for high-risk patients (HR-II) of the 1995 protocol of the German Leukemia Treatment Group (BFM95) for acute lymphoid leukemia

Drug	Administration	Dose	Days
Dexamethasone	IV	20 mg/m^2/day (to divide in doses given every 12 h)	D1 to D5
Methotrexate	IV in 24 h	5000 mg/m^2/day	D1
Rescue with Leucovorin	First IV, then oral.	Initial dose: 30 mg/m^2/dose; afterward, give five doses every 3 h, at 15 mg/m^2/dose. Then 15 mg/m^2/dose orally every 6 h until the serum level is $<5 \times 10^{-8}$M	First dose is 36 h after the initiation of MTX.
Ifosfamide	IV in 1 h	800 mg/m^2/dose	D2 and D3 every 12 h, D4 single dose.
Mesna	IV	300 mg/m^2/dose	Hours 0, 4, and 8 after initiation of ifosfamide. Use this scheme every day of ifosfamide treatment.

(continued)

Table 3.42 (continued)

Drug	Administration	Dose	Days
L-Asparaginase	IV in 6 h	25,000 IU/m^2/day	D6
Vinblastine*	IV	6 mg/m^2/day	D1, D6
Daunorubicin	IV in 24 h	30 mg/m^2/day	D5
MADIT	IT	Up to 1 year old: 6 mg of methotrexate, 16 mg of cytarabine, 2 mg/m^2 of dexamethasone. 1–2 years old: 8 mg of MTX, 20 mg of ARA-C, 2 mg/m^2 of DEXA. 2–3 years old: 10 mg of MTX, 26 mg of Ara-C, 2 mg/m^2 of DEXA. > 3 years old: 12 mg of MTX, 30 mg of Ara-C, 2 mg/m^2 of DEXA.	D1

Source: Based on information from Möricke et al. [117] and Busato et al. [7]
*Vindesine IV (3 mg/m^2/day, in a maximum of 5 mg), on D1 and 6, is used in some institutions instead of vinblastine [117].
Each HR protocol, in the study, was given twice [117].

Table 3.43 Therapy III for high-risk patients (HR-III) of the 1995 protocol of the German Leukemia Treatment Group (BFM95) for acute lymphoid leukemia

Drug	Administration	Dose	Days
Dexamethasone	IV	20 mg/m²/day (to divide in doses given every 12 h)	D1 to D5
L-Asparaginase	IV	25,000 IU/m²/day	D6
Cytarabine	IV in 3 hours	2000 mg/m²/dose (every 12 h)	D1, D2 (total of 4 doses)
Etoposide	IV in 1 hour	100 mg/m²/dose (every 12 h)	D3, D4, D5 (total of 5 doses)
MADIT	IT	Up to 1 year old: 6 mg of methotrexate, 16 mg of cytarabine, 2 mg/m² of dexamethasone. 1–2 years old: 8 mg of MTX, 20 mg of Ara-C, 2 mg/m² of DEXA. 2–3 years old: 10 mg of MTX, 26 mg of Ara-C, 2 mg/m² of DEXA. >3 years old: 12 mg of MTX, 30 mg of Ara-C, 2 mg/m² of DEXA.	D5

Source: Based on information from Möricke et al. [117] and Busato et al. [7]
Each HR protocol, in the study, was given twice [117].

After the end of Phase II re-induction, there is an interval of 2 weeks and then the maintenance phase (Tables 3.44–3.45) starts. Patients should be in remission to enter this phase (maintenance), and this phase is indicated for patients in all risk groups.

BFM95: Protocol of the German Group for Leukemia Treatment: Maintenance for Low- and High-risk Patients:

- High-risk patients and low-risk girls: Duration of 24 months (from the beginning of protocol I).
- Low-risk boys: Duration of 36 months (from the beginning of protocol I).

In protocol study, maintenance was given from end of intensive chemotherapy until 104 weeks after diagnosis; for low-risk boys until 156 weeks [117].

Table 3.44 Maintenance therapy of the 1995 protocol of the German Leukemia Treatment Group (BFM95) for acute lymphoid leukemia

Drug	Administration	Dose
Mercaptopurine	Oral	50 mg/m^2/day
Methotrexate	Oral	20 mg/m^2/week (in a single dose)

Source: Based on information from Möricke et al. [117] and Busato et al. [7]

- Medium-risk patients: Duration of 24 months (from the beginning of protocol I) [7].

Table 3.45 Maintenance therapy, for medium-risk randomized into MR-B patients, of the 1995 protocol of the German Leukemia Treatment Group (BFM95) for acute lymphoid leukemia

Drug	Administration	Dose
Mercaptopurine	Oral	50 mg/m^2/day
Methotrexate	Oral	20 mg/m^2/week (in a single dose)
Dexamethasone*	Oral	6 mg/m^2/day for 7 days
Vincristine*	IV	1.5 mg/m^2/day on D1 and on D7 (maximum dose per day is 2 mg)

Source: Based on information from Möricke et al. [117] and Busato et al. [7]

*Six pulses of dexamethasone and vincristine were given, in the study, every 10 weeks.

3.4.2 Therapy for Low-Risk Patients with the Protocol of the Brazilian Childhood Cooperative Group of 1999 (GBTLI ALL-99)

At diagnosis, if the patient has one or more of the following characteristics, they should be classified as having a high risk of recurrence: age below 12 months or above 10 years, white blood cell count higher than 50,000/mm^3, or the presence of unfavorable karyotypic alterations [64].

Regarding the evaluation of early response, some data using a blast cell count of less than 1000/mm^3 on day 7 has been used in clinical screening to define patients who are poor responders in the BFM protocols. The global white blood cell count on day 7 has been used in the evaluation of early treatment response, for risk stratification, in the GBTLI-99 protocol, because in patients of GBTLI-93 protocol, a significant association with poor outcome has been established, when showing a white blood cell count of >5000/mm^3, was associated with a low 5-year event-free survival [64].

High multidrug resistance gene complex (MDR) levels (10^{-2} to 10^{-3}) on day 15 and during weeks 5 and 12 of the induction of this protocol are associated with an unfavorable prognosis. The most important prognostic factors are associated with age, MDR detection on day 28, diagnosis, white blood cell count on day 7, risk group classification, immunophenotyping, and morphological bone marrow status on day 28 [64].

Clonal immunoglobulin H (IgH) and T-cell receptor (TCR) rearrangements, detected by polymerase chain reaction (PCR) and homo/heteroduplex analysis, seem to provide the most important independent prognostic analysis and the method is rapid and cheap. This method, however, is not truly quantitative and, due to its lower sensitivity, the lack of detection of rearrangement after induction therapy does not conclusively represent the absence of relapse, and can be considered only to identify patients with high residual tumor load. The use of simplified methods for the evaluation of an early response proved to be a good predictor of an unfavorable course in children with ALL and could be used to stratify treatment, especially in low-budget institutions [64].

Table 3.46 First induction phase of the Brazilian Childhood Cooperative Group protocol of 1999, GBTLI ALL-99, for low-risk patients with acute lymphoid leukemia

Drug	Administration	Dose	Days
Prednisone[a]	Oral	40 mg/m^2/day	D1 to D28
Vincristine	IV	1.5 mg/m^2/day (maximum 2 mg)	D0, 7, 14, and 21
Daunorubicin	IV in 1 h	25 mg/m^2/dose	D0, 7, 14, and 21
L-Asparaginase	IM	5000 IU/m^2/dose	D3, 5, 7, 9, 11, 13, 15, 17, and 19
IT (With methotrexate, cytarabine, and hydrocortisone, all intrathecally)	IT	According to age	D0, 14, and 28. If CNS+, give in addition, on days 7 and 21.

Source: Based on information from Brandalise et al. [65]
[a]The initial protocol proposed dexamethasone orally at a dose of 6 mg/m^2/day for 28 days; it was then modified to prednisone orally at a dose of 40 mg/m^2/day for 28 days, as mentioned here. Prednisone has considerably reduced the rate of infections and deaths during induction [65].

This phase has a duration of 4 weeks [65].

Table 3.47 Second induction phase of the Brazilian Childhood Cooperative Group protocol of 1999, GBTLI ALL-99, for low-risk patients with acute lymphoid leukemia

Drug	Administration	Dose	Days
Cyclophosphamide	IV in 1 h	1 g/m^2	Just one dose
Mesna	IV	300 mg/m^2/dose	Hours 0 and 4 after initiation of cyclophosphamide infusion

(continued)

Table 3.47 (continued)

Drug	Administration	Dose	Days
Cytarabine	SC	75 mg/m²/dose	Four doses weekly, between D 29–32 and D 36–40 (D36 to 40 is the period, but should be done just 4 doses, not 5).
Mercaptopurine	Oral	50 mg/m²/dose	D28 to D42

Source Based on information from Brandalise et al. [65]

This phase has a duration of 4 weeks [65].

Table 3.48 Intensification phase of the Brazilian Childhood Cooperative Group protocol of 1999, GBTLI ALL-99, for low-risk patients with acute lymphoid leukemia

Drug	Administration	Dose	Days
Methotrexate	IV in 6 h	2 g/m²/dose	Once every 2 weeks
Folinic acid (for rescue)	IV	15 mg/m²/dose	At hours 36, 42, 48, and 54 after initiation of MTX dose.
Mercaptopurine	Oral	50 mg/m²/day	During 8 weeks.
IT (With methotrexate, cytarabine, and hydrocortisone, all intrathecally)	IT	According to age	1 week after MTX IV infusion. Give four doses.

Source: Based on information from Brandalise et al. [65]

This phase has a duration of 8 weeks [65].

Table 3.49 Late consolidation first phase of the Brazilian Childhood Cooperative Group protocol of 1999, GBTLI ALL-99, for low-risk patients with acute lymphoid leukemia

Drug	Administration	Dose	Days
Dexamethasone	Oral	6 mg/m^2/day	For 7 days per week. Give at weeks 14, 16, and 18
Vincristine	IV	1.5 mg/m^2/dose (maximum 2 mg)	Weekly, at weeks 14 through 18
Doxorubicin	IV in 1 h	30 mg/m^2/dose	One dose at week 15 and one dose at week 17
L-Asparaginase	IM	5000 IU/m^2/dose	Every other day for four doses, start at week 15
IT (With methotrexate, cytarabine, and hydrocortisone, all intrathecally)	IT	According to age	One dose at week 14 and one dose at week 18

Source: Based on information from Brandalise et al. [65]

This phase has a duration of 4 weeks [65].

Table 3.50 Late consolidation second phase of the Brazilian Childhood Cooperative Group protocol of 1999, GBTLI ALL-99, for low-risk patients with acute lymphoid leukemia

Drug	Administration	Dose	Days
Cyclophosphamide	IV in 1 h	1 g/m^2/dose	Just one dose
Mesna	IV	300 mg/m^2/dose	Hours 0 and 4 after initiation of cyclophosphamide infusion
Cytarabine	SC	75 mg/m^2/dose	Four doses weekly, at weeks 19, 20, and 21.
Thioguanine	Oral	60 mg/m^2/dose	Start at week 19, give for 21 days
IT (With methotrexate, cytarabine, and hydrocortisone, all intrathecally)	IT	According to age	One dose at week 22.

Source: Based on information from Brandalise et al. [65]

This phase has a duration of 4 weeks [65].

In the original study, for the next phase, maintenance, patients were randomized into two groups, those with continuous 6-mercaptopurine and methotrexate (Group 1) and those with intermittent treatment with these agents (Group 2). Only the group with better results is described in this book. Group 2 (intermittent group) had better results, because, in maintenance, according to the protocol study, the intermittent regimen of 6-mercaptopurine and methotrexate is a less toxic regimen and with a trend toward better long-term event-free survival. Patients in this group had lower rates of severe grades (3 and 4) of hepatic and hematological toxicities, and a lower death rate in remission than those receiving the continuous therapy. Boys allocated to the intermittent regimen had significantly better event-free survival than patients in Group 1 (receiving continuous therapy) [65].

Table 3.51 Maintenance therapy with intermittent 6-mercaptopurine and methotrexate, in the Brazilian Childhood Cooperative Group protocol of 1999, GBTLI ALL-99, for low-risk patients with acute lymphoid leukemia

Drug	Administration	Dose	Days
6-Mercaptopurine	Oral	100 mg/m^2/day (maximum 175 mg)	For 10 days, with 11 days rest. Give 24 h after MTX infusion
Methotrexate	IV in 6 h	200 mg/m^2/dose	Every 3 weeks
Folinic acid (for rescue)	IV	5 mg/m^2/dose	At hours 36 and 42 after initiation of MTX infusion

(continued)

Table 3.51 (continued)

Drug	Administration	Dose	Days
Dexamethasone	Oral	4 mg/m^2/dose	Three doses, each one every other day. Give this scheme every 8 weeks until week 72
Vincristine	IV	1.5 mg/m^2/dose (maximum 2 mg)	D1. Give this every 8 weeks until week 72
IT (With methotrexate, cytarabine, and hydrocortisone, all intrathecally)	IT	According to age	

Source: Based on information from Brandalise et al. [65]

3.4.3 *Protocol of the Berlin-Frankfurt-Münster Group, ALL IC-BFM 2002, for Acute Lymphoid Leukemia*

The intention of Intercontinental-BFM 2002 study was to explore the impact of differential delayed intensification in all risk groups.

The conclusion reached by the International Berlin-Frankfurt-Münster Group was that the ALL IC-BFM 2002 trial was a good example of international collaboration in pediatric oncology, and although the alternative delayed intensification did not improve outcome compared with standard treatment, and the overall results were worse than those achieved by longer established leukemia groups, the national results have generally improved [88].

Regarding stratification, for the ALL IC-BFM 2002 study, patients were divided into three risk groups [88]:

1. Standard risk, defined as good prednisone response, age ≥1 year to younger than 6 years, initial white blood cell count less than 20×10^9/L, and M1 [<5 % blasts] or M2 [≥5 % to <25 % blasts] marrow on day 15, and M1 marrow on day 33. All criteria must be fulfilled.
2. Intermediate risk (IR), defined as good prednisone response, patients aged younger than 1 year or age 6 years or older, and/or white blood cell count $\geq 20 \times 10^9$/L and M1 or M2 marrow on day 15 and M1 marrow on day 33, or standard-risk criteria, but M3 (≥25 % blasts) marrow on day 15 and M1 marrow on day 33.
3. High risk (HR), defined as at least one of the following: poor prednisone response, intermediate risk and M3 marrow on day 15, M2 or M3 marrow on day 33, t(9;22) (BCR-ABL), or t(4;11) (MLL-AF4).

Regarding the treatment, for standard-risk patients classified by B-cell precursor ALL, two doses of daunorubicin were given in the protocol study, in induction, compared with the four doses given for all other patients in this study. In consolidation, a high dose of methotrexate (5 g/m^2) was administered for standard-risk/intermediate-risk T-cell ALL patients, and 2 g/m^2 of methotrexate was administered for standard-risk/intermediate-risk B-cell precursor ALL patients [88].

Consolidation for high-risk patients consisted of three intensive polychemotherapy blocks. In the study, immediately on consolidation, patients were randomly allocated 1:1 to the experimental arm or to the control arm of delayed intensification, stratified by risk group and country, by using randomization lists [88].

Delayed intensification started 2 weeks after patient reallocation. In the standard-risk group, protocol III was repeated twice in 12 weeks apart in the standard-risk-2 experimental arm; although a single protocol II was given in the standard risk-1 control arm. In the intermediate-risk group, protocol III was given three times in 6 weeks apart, in the intermediate-risk-2 experimental arm; and a single protocol II was given in the intermediate-risk-1 control arm [88].

In high-risk patients, the high-risk-1 experimental arm was tested with identical protocol than intermediate risk. For patients of high-risk-2A experimental arm, protocol II was given twice in 6 weeks apart. For high-risk-2B patients was given three high-risk blocks plus one protocol II. The choice for the high-risk control arm was up to each national group according to its own experience. Only T-ALL and high-risk patients aged $\geq$ 1 year received prophylactic cranial radiotherapy, of 12 Gy. Therapeutic cranial radiotherapy was reserved for patients with initial CNS involvement and was given at an age-adjusted dosage; none for infants younger than 1 year, 12 Gy for children aged 1 to younger than 2 years, and 18 Gy for children aged 2 years or more [88].

Allogeneic hematopoietic stem-cell transplantation from a matched sibling donor was recommended for very high-risk patients, defined as those with no complete remission by day 33, high-risk plus M3 on day 15, Philadelphia chromosome-positive ALL, poor prednisone response plus any of T-ALL, pro-B ALL (very early CD10- B-cell precursor ALL), white blood cell count more than 100×10^9/L, or t(4;11) (MLL-AF4) [88].

Table 3.52 Phase I of protocol I' (standard-risk B-cell precursor ALL only) and protocol I (standard-risk T-cell ALL, all intermediate-risk and high-risk patients) of induction therapy of the ALL IC-BFM 2002 protocol, elaborated by the Berlin-Frankfurt-Münster Group, for acute lymphoid leukemia patients

Drug	Administration	Dose	Days
Prednisone	Oral	60/mg/m^2/day	D1 to 28
Vincristine	IV push	1.5 mg/m^2/day (maximum dose is 2 mg)	D8, 15, 22, and 29
Daunorubicin	IV in 1 h	30 mg/m^2	D8, 15, 22,[a] and 29[a]
L-Asparaginase	IV in 1 h	5000 IU/m^2	D12, 15, 18, 21, 24, 27, 30, and 33
Methotrexate	IT	12 mg (Adjust for children younger than 3 years old)	D1, 12, and 33[b]

Source: Based on information from Stary et al. [88]

[a]In standard-risk B-cell ALL, daunorubicin on days 22 and 29 was omitted in the protocol study [88].

[b]In the protocol study, additional doses of methotrexate IT were delivered on days 18 and 27 for patients with CNS status 2 and 3 [88].

Table 3.53 Phase II of protocol I' (standard-risk B-cell precursor ALL only) and protocol I (standard-risk T-cell ALL, all intermediate-risk and high-risk patients) of induction therapy of the ALL IC-BFM 2002 protocol, elaborated by the Berlin-Frankfurt-Münster Group, for acute lymphoid leukemia patients

Drug	Administration	Dose	Days
Cyclophosphamide	IV in 1 h	1000 mg/m^2/day	D36 and D64
Cytarabine	IV push	75 mg/m^2/day	D38 to 41, D45 to 48, D52 to 55, and D59 to 62.
6-Mercaptopurine	Oral	60 mg/m^2/day	D36 to 63
Methotrexate	IT	12 mg/m^2 (Adjust for children younger than 3 years old)	D45 and D59

Source: Based on information from Stary et al. [88]

Table 3.54 Protocol mM (B-cell precursor ALL, standard and intermediate risks only) of consolidation therapy of the ALL IC-BFM 2002 protocol, elaborated by the Berlin-Frankfurt-Münster Group, for acute lymphoid leukemia patients

Drug	Administration	Dose	Days
6-Mercaptopurine	Oral	25 mg/m^2/day	D1 to 56
Methotrexate	IV in 24 h (10 % over 30 min, and the remaining 90 % over 23.5 h)	2000 mg/m^2/dose	D8, 22, 36, and 50
Rescue with Leucovorin	IV	15 mg/m^2/dose	Hours 42, 48, and 54 after the initiation of MTX[a]
Methotrexate	IT	12 mg (Adjust for children younger than 3 years old)	D8, 22, 36, and 50

Source: Based on information from Stary et al. [88]
[a]Increase leucovorin dose if methotrexate level at hour 42 or later is >1.0 μmol/L. If methotrexate level at hour 54 is >0.25 μmol/L, rescue may be continued at 6-h intervals until methotrexate levels reach ≤0.25 μmol/L.

Table 3.55 Protocol M (T-cell ALL, standard and intermediate risks only) of consolidation therapy of the ALL IC-BFM 2002 protocol, elaborated by the Berlin-Frankfurt-Münster Group, for acute lymphoid leukemia patients

Drug	Administration	Dose	Days
6-Mercaptopurine	Oral	25 mg/m^2/day	D1 to 56
Methotrexate	IV in 24 h (10 % over 30 min, and the remaining 90 % over 23.5 h)	5000 mg/m^2/dose	D8, 22, 36, and 50
Rescue with Leucovorin	IV	15 mg/m^2/dose	Hours 42, 48, and 54 after the initiation of MTX[a]
Methotrexate	IT	12 mg (Adjust for children younger than 3 years old)	D8, 22, 36, and 50

Source: Based on information from Stary et al. [88]

[a]Increase leucovorin dose if methotrexate level at hour 42 or later is >1.0 μmol/L. If methotrexate level at hour 54 is >0.25 μmol/L, rescue may be continued at 6-h intervals until methotrexate level reaches ≤0.25 μmol/L.

Table 3.56 Block HR-1' (all high-risk patients) of consolidation therapy of ALL IC-BFM 2002 protocol, elaborated by the Berlin-Frankfurt-Münster Group, for acute lymphoid leukemia patients

Drug	Administration	Dose	Days
Dexamethasone	Oral or IV	20 mg/m²/day	D1 to 5
Vincristine	IV	1.5 mg/m²/day (maximum of 2 mg)	D1 and D6
Methotrexate	IV in 24 h (10 % over 30 min, and the remaining 90 % over 23.5 h)	5000 mg/m²	D1
Rescue with Leucovorin	IV	15 mg/m²/dose	Hours 42, 48, and 54 after the initiation of MTX[a]
Cyclophosphamide	IV in 1 h	200 mg/m²/dose	Start on D2, give every 12 h, until completion of five doses
Cytarabine	IV in 3 h	2000 mg/m²/dose	Start on D5, give every 12 h, until completion of two doses
L-Asparaginase	IV in 2 h	25,000 IU/m²/day	D6 and D11
Methotrexate, cytarabine, and prednisolone	IT	MTX 12 mg, Ara-C 30 mg, prednisolone 10 mg (adjust for children younger than 3 years old)	D1

Source: Based on information from Stary et al. [88]

[a]Increase leucovorin dose if methotrexate level at hour 42 or later is >1.0 μmol/L. If methotrexate level at hour 54 is >0.25 μmol/L, rescue may be continued at 6-h intervals until methotrexate level reaches ≤0.25 μmol/L.

Table 3.57 Block HR-2' (all high-risk patients) of consolidation therapy of ALL IC-BFM 2002 protocol, elaborated by the Berlin-Frankfurt-Münster Group, for acute lymphoid leukemia patients

Drug	Administration	Dose	Days
Dexamethasone	Oral or IV	20 mg/m^2/day	D1 to 5
Vindesine	IV	3 mg/m^2/day (maximum of 5 mg)	D1 and 6
Methotrexate	IV in 24 h (10 % over 30 min, and the remaining 90 % over 23.5 h)	5000 mg/m^2	D1
Rescue with Leucovorin	IV	15 mg/m^2/dose	Hours 42, 48, and 54 after the initiation of MTX[a]
Ifosfamide	IV in 1 h	800 mg/m^2/dose	Start at D2 and give every 12 h until completion of five doses
Daunorubicin	IV in 24 h	30 mg/m^2/day	D5
L-Asparaginase	IV in 2 h	25,000 IU/m^2/day	D6 and D11
Methotrexate, cytarabine, and prednisolone	IT	MTX 12 mg, Ara-C 30 mg, prednisolone 10 mg (adjust for children younger than 3 years old)	D1[a]

Source: Based on information from Stary et al. [88]
[a]Patients with CNS disease status 3 may be given an additional dose on day 5.

Table 3.58 Block HR-3' (all high-risk patients) of consolidation therapy of ALL IC-BFM 2002 protocol, elaborated by the Berlin-Frankfurt-Münster Group, for acute lymphoid leukemia patients

Drug	Administration	Dose	Days
Dexamethasone	Oral or IV	20 mg/m^2	D1 to 5
Cytarabine	IV in 3 h	2000 mg/m^2/dose	Start at D1, give every 12 h until four doses completed
Etoposide	IV in 1 h	100 mg/m^2/dose	Start at D3, give every 12 h until five doses completed
L-Asparaginase	IV in 2 h	25,000 IU/m^2/day	D6 and D11
Methotrexate, cytarabine, and prednisolone	IT	MTX 12 mg, Ara-C 30 mg, prednisolone 10 mg (adjust for children younger than 3 years old)	D5

Source: Based on information from Stary et al. [88]

In the study of the ALL IC-BFM 2002 protocol, protocol II was given once for standard-risk-1 and intermediate-risk-1 patients as the only delayed intensification element; for patients who had been classified as high-risk 2A, protocol II was given twice, with one 4-week interim maintenance therapy in between; and in the high-risk 2B group, protocol II was given once after they had completed a series of three HR blocks [88].

Table 3.59 Delayed intensification phase I of protocol II (for standard-risk 1, intermediate-risk 1, high-risk 2A, and high-risk 2B) of ALL IC-BFM 2002 protocol, elaborated by the Berlin-Frankfurt-Münster Group, for acute lymphoid leukemia patients

Drug	Administration	Dose	Days
Dexamethasone	Oral or IV	10 mg/m^2/day	D1 to 21
Vincristine	IV	1.5 mg/m^2/day (maximum dose is 2 mg)	D8, D15, D22, and D29
Doxorubicin	IV in 1 h	30 mg/m^2/day	D8, D15, D22, and D29
L-Asparaginase	IV in 1 h	10,000 IU/m^2/day	D8, D11, D15, D18

Source: Based on information from Stary et al. [88]

Table 3.60 Delayed intensification phase II of protocol II (for standard-risk 1, intermediate risk 1, high-risk 2A, and high-risk 2B) of ALL IC-BFM 2002 protocol, elaborated by the Berlin-Frankfurt-Münster Group, for acute lymphoid leukemia patients

Drug	Administration	Dose	Days
Cyclophosphamide	IV in 1 h	1000 mg/m^2/day	D36
Cytarabine	IV in bolus	75 mg/m^2/day	D38 to 41 and D45 to 48
6-Thioguanine	Oral	60 mg/m^2/day	D36 to 49
Methotrexate	IT	12 mg (Adjust for children younger than 3 years old)	D38 and D45[a]

Source: Based on information from Stary et al. [88]
[a]Patients with initial CNS disease status 3 may receive additional methotrexate IT on days 1 and 18.

Table 3.61 Delayed intensification phase I of protocol III (for standard-risk 2, intermediate-risk 2, and high-risk 1) of ALL IC-BFM 2002 protocol, elaborated by the Berlin-Frankfurt-Münster Group, for acute lymphoid leukemia patients

Drug	Administration	Dose	Days
Dexamethasone	Oral or IV	10 mg/m^2/day	D1 to 14
Vincristine	IV	1.5 mg/m^2/day (maximum of 2 mg)	D1 and D8
Doxorubicin	IV in 1 h	30 mg/m^2/day	D1 and D8
L-Asparaginase	IV in 1 h	10,000 IU/m^2/day	D1, D4, D8, and D11

Source: Based on information from Stary et al. [88]

Table 3.62 Delayed intensification phase II of protocol III (for standard-risk 2, intermediate-risk 2, and high-risk 1) of ALL IC-BFM 2002 protocol, elaborated by the Berlin-Frankfurt-Münster Group, for acute lymphoid leukemia patients

Drug	Administration	Dose	Days
Cyclophosphamide	IV in 1 h	500 mg/m^2/day	D15
Cytarabine	IV	75 mg/m^2/day	D17 to 20, and D24 to 27
6-Thioguanine	Oral	60 mg/m^2/day	D15 to 28
Methotrexate	IT	12 mg (Adjust for children younger than 3 years old)	D17 and D24[a]

Source: Based on information from Stary et al. [88]
[a]Patients with initial CNS disease status 3 may receive additional methotrexate IT on day 1.

Protocol III was given twice for standard-risk-2 arm with one 10-week interim maintenance therapy between each protocol III. For arms intermediate-risk-2 and high-risk-1, protocol III was given 3 times, with two 4-week interim maintenance between each protocol III.

The only delayed intensification that arm HR-2B patients receive is performing block HR-1', HR-2', or HR-3', as in HR consolidation (see tables 3.56, 3.57 and 3.58). In total, arm HR-2B perform six HR blocks: first on consolidation (as another groups), then, as part of delayed intensification therapy [88].

Interim maintenance therapy started (see Table 3.63 below) 1 week after the end of the intensive therapy element, and finished 1 week before the next intensive therapy [88].

Table 3.63 Interim maintenance therapy of ALL IC-BFM 2002 protocol, elaborated by the Berlin-Frankfurt-Münster Group, for acute lymphoid leukemia patients

Drug	Administration	Dose	Days
Methotrexate	Oral	20 mg/m^2/week (Adjust according to WBC; target, 2000–3000/μL)	Once per week
6-Mercaptopurine	Oral	50 mg/m^2/day (Adjust according to WBC; target, 2000–3000/μL)	Once per day

Source: Based on information from Stary et al. [88]

The next phase, maintenance therapy, in the original protocol was started 2 weeks after the end of the intensive therapy and was given until 104 weeks from diagnosis [88].

Table 3.64 Maintenance therapy of ALL IC-BFM 2002 protocol, elaborated by the Berlin-Frankfurt-Münster Group, for acute lymphoid leukemia patients

Drug	Administration	Dose	Days
Methotrexate	Oral	20 mg/m^2/week (Adjust according to WBC; target, 2000–3000/μL)	Once per week
6-Mercaptopurine	Oral	50 mg/m^2/day (Adjust according to WBC; target, 2000–3000/μL)	Once per day

Source: Based on information from Stary et al. [88]

3.5 Brain Tumors

It can be difficult to treat some brain tumors with chemotherapy drugs because the blood-brain barrier only allows certain substances through from the blood to the brain tissues. Some drugs can cross the blood-brain barrier, and some brain tumors damage the blood-brain barrier, thus allowing the chemotherapy drug to enter [112].

According to Cancer Research UK, children less than 3 years old with primitive neuroectodermal tumours (PNETs), ependymomas, or gliomas may have chemotherapy instead of radiotherapy. They will have the same chemotherapy drugs repeated every week for up to 2 years, to reduce the long-term side effects that radiotherapy can have in very young children. Once the child is over 3 years old, they can have radiotherapy. For some types of brain tumors in children, chemotherapy can work very well, and it is then possible to avoid giving radiotherapy altogether after a year or more of chemotherapy [112].

3.5.1 High-Dose Protocol: Cyclophosphamide, Doxorubicin, and Vincristine (HD-CAV) (Neuroblastoma) [63]

This protocol, with an intensive regimen of high doses of cyclophosphamide, doxorubicin, and vincristine, is used in children with recurrent refractory solid tumors with poor prognosis.

Table 3.65 Protocol of high-dose – cyclophosphamide, doxorubicin, and vincristine (HD-CAV)

Drug	Administration	Dose	Day
Cyclophosphamide	IV	70 mg/kg/dose	D1 and D2
Doxorubicin	IV	25 mg/m^2/dose	D1 to 3
Vincristine[a]	IV	1 mg/m^2/dose	D1 to 3
Vincristine[a]	IV	1.5 mg/m^2	D9

Source: Based on information from Zouber et al. [63]

[a]Maximum dose of vincristine is 2 mg; never exceed this dose.

3.5.2 Cyclophosphamide, Vincristine, Cisplatin, and Etoposide (COPE/Baby Brain I) [4]

Repeat the cycle every 28 days in the sequence: cycle A, cycle A, cycle B, cycle A, cycle A, cycle B.

Table 3.66 Cycle A of protocol with cyclophosphamide, vincristine, cisplatin, and etoposide (COPE/Baby Brain I)

Drug	Administration	Dose	Days
Vincristine	IV	0.065 mg/kg/day (to a maximum dose of 1.5 mg)	D1 and 8
Cyclophosphamide	IV	65 mg/kg/day	D1

Source: Based on information from Bragalone [4]

Table 3.67 Cycle B of protocol with cyclophosphamide, vincristine, cisplatin, and etoposide (COPE/Baby Brain I)

Drug	Administration	Dose	Days
Cisplatin	IV	4 mg/kg/day	D1
Etoposide	IV	6.5 mg/kg/day	D3 and 4

Source: Based on information from Bragalone [4]

3.5.3 *Eight in One (8 in 1) [4]*

Protocol with two variations.

Table 3.68 Protocol 8 in 1 – variation 1

Drug	Administration	Dose	Days
Methylprednisolone	IV	300 mg/m² every 6 h (total of three doses)	D1
Vincristine	IV	1.5 mg/m² (maximum dose of vincristine = 2 mg)	D1
Lomustine	Oral	75 mg/m²	D1
Procarbazine	Oral	75 mg/m²	D1 (1 h after methylprednisolone and vincristine)
Hydroxyurea	Oral	3000 mg/m²	D1 (2 h after methylprednisolone and vincristine)
Cisplatin	IV	90 mg/m²	D1 (3 h after methylprednisolone and vincristine)
Cytarabine	IV	300 mg/m²	D1 (9 h after methylprednisolone and vincristine)
Dacarbazine	IV	150 mg/m²	D1 (12 h after vincristine and methylprednisolone)

Source: Based on information from Bragalone [4]

Repeat the cycle every 14 days.

Table 3.69 Protocol 8 in 1 – variation 2

Drug	Administration	Dose	Days
Methylprednisolone	IV	300 mg/m^2 every 6 h (total of three doses)	D1
Vincristine	IV	1.5 mg/m^2 (maximum dose of vincristine = 2 mg)	D1
Lomustine	Oral	75 mg/m^2	D1
Procarbazine	Oral	75 mg/m^2	D1 (1 h after vincristine and methylprednisolone)
Hydroxyurea	Oral	3000 mg/m^2	D1 (2 h after vincristine and methylprednisolone)
Cisplatin	IV	60 mg/m^2	D1 (3 h after vincristine and methylprednisolone)
Cytarabine	IV	300 mg/m^2	D1 (9 h after vincristine and methylprednisolone)
Cyclophosphamide	IV	300 mg/m^2	D1 (12 h after vincristine and methylprednisolone)

Source: Based on information from Bragalone [4]

Repeat the cycle every 14 days.

3.5.4 Cyclophosphamide, Doxorubicin, Vincristine, Cisplatin, and Etoposide (CAV-P/VP) (Neuroblastoma) [4]

Table 3.70 Cycles 1, 2, 4, and 6 of protocol with cyclophosphamide, doxorubicin, vincristine, cisplatin, and etoposide (CAV-P/VP)

Drug	Administration	Dose	Days
Cyclophosphamide	IV	70 mg/kg/day	D1 and 2
Doxorubicin	IV in continuous infusion	25 mg/m^2/day	D1, 2, and 3
Vincristine[a]	IV in continuous infusion	0.033 mg/kg/day	D1, 2, and 3
Vincristine[a]	IV	1.5 mg/m^2	D9

Source: Based on information from Bragalone [4]
[a]Maximum dose of vincristine is 2 mg; never exceed this dose.

Table 3.71 Cycles 3, 5, and 7 of protocol with cyclophosphamide, doxorubicin, vincristine, cisplatin, and etoposide (CAV-P/VP)

Drug	Administration	Dose	Days
Etoposide	IV	200 mg/m^2/day	D1, 2, and 3
Cisplatin	IV	50 mg/m^2/day	D1 to 4

Source: Based on information from Bragalone [4]

3.6 Wilms Tumor

The prognosis is excellent; more than 85 % of children are cured. These tumors are very sensitive to chemotherapy and radiation [116].

3.6.1 Doxorubicin, Vincristine, and Dactinomycin (AVD) [4]

Table 3.72 Protocol with doxorubicin, vincristine, and dactinomycin (AVD)

Drug	Administration	Dose	Days
Dactinomycin	IV	15 μg/kg/day	D1 to 5 of weeks 0, 13, 26, 39, 52, and 65
Doxorubicin	IV	60 mg/m^2/day	D1 of weeks 6, 19, 32, 45, and 58
Vincristine	IV	1.5 mg/m^2/day (maximum dose of 2 mg/day)	D1 of weeks 1 to 8, 13, 14, 26, 27, 39, 40, 52, 53, 65, and 66

Source: Based on information from Bragalone [4]

3.6.2 Dactinomycin and Vincristine (AV) (Stage IV and Favorable Histology) [4]

Table 3.73 Protocol with dactinomycin and vincristine (AV)

Drug	Administration	Dose	Days
Dactinomycin	IV	15 μg/kg/day	D1 to 5 of weeks 0, 13, 26, 39, 52, and 65
Vincristine	IV	1.5 mg/m^2/day (maximum dose of 2 mg/day)	D1 of weeks 1 to 8, 13, 14, 26, 27, 39, 40, 52, 53, 65, and 66

Source: Based on information from Bragalone [4]

3.7 Retinoblastoma

Treatment may be individualized and depends on various factors, and treated children are at high risk of cosmetic and functional impairment related to enucleation and radiation [115].

Children with a heritable mutation in the RB1 gene have a high rate of secondary malignancy after radiation therapy [115].

3.7.1 Cyclophosphamide, Cisplatin, Doxorubicin, and Etoposide (CCDE) [4]

Table 3.74 Protocol with cyclophosphamide, cisplatin, doxorubicin, and etoposide (CCDE)

Drug	Administration	Dose	Days
Cyclophosphamide	IV	150 mg/m^2/day	D1 to 7
Cyclophosphamide	Oral	150 mg/m^2/day	D22 to 28 and D43 to 49
Doxorubicin	IV	35 mg/m^2/day	D10 and 52
Cisplatin	IV	90 mg/m^2/day	D8, 50, and 71
Etoposide	IV in continuous infusion	150 mg/m^2/day	D29 to 31 and D73 to 75

Source: Based on information from Bragalone [4]

3.8 Non-Hodgkin Lymphoma

These tumors are very sensitive to chemotherapy. Multidrug regimens, similar to those used for leukemia, are recommended. Therapy may begin with surgical resection in cases of primary gastrointestinal tumors that are amenable to complete resection [114].

Table 3.75 Non-Hodgkin lymphoma: cyclophosphamide, vincristine, doxorubicin, and methotrexate (CODOX-M) [4]

Drug	Administration	Dose	Days
Cyclophosphamide	IV	800 mg/m^2	D1
Cyclophosphamide	IV	200 mg/m^2	D2 to 5
Vincristine	IV	1.5 mg/m^2 (maximum dose of vincristine is 2 mg/day)	D1 and 8
Doxorubicin	IV	40 mg/m^2	D1
Methotrexate	IV in 1 h	1200 mg/m^2[a]	D10
Methotrexate	IV in 23 h	240 mg/m^2/h, during 23 h[a]	D10
Folinic acid	IV	192 mg/m^2/dose	D11 (start 36 h after beginning of MTX)
Folinic acid	IV	12 mg/m^2/dose	D11 every 6 h until serum level of MTX is $<5 \times 10^{-8}$M
Cytarabine	IT	70 mg (if <3 years old, adjust the dose according to age)	D1
Methotrexate	IT	12 mg (if <3 years old, adjust the dose according to age)	D3

Source: Based on information from Bragalone [4]
[a]Total methotrexate IV on cycle is 6720 mg/m^2.

Repeat the cycle when the absolute neutrophil count is >1000/m^2; total of three cycles.

3.9 High-Risk Central Nervous System B Non-Hodgkin Lymphoma and B Acute Lymphoblastic Leukemia: Protocol of the French Society of Pediatric Oncology LMB86

Table 3.76 COP phase of protocol for high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia treatment, of the French Society of Pediatric Oncology LMB86

Drug	Administration	Dose	Days
Cyclophosphamide	IV	300 mg/m^2	D1
Vincristine	IV	1 mg/m^2 (maximum dose of vincristine = 2 mg)	D1
Prednisone	IV or Oral	60 mg/m^2/day (divided into two doses per day)	D1 to 7
Methotrexate, hydrocortisone, and cytarabine	IT	MTX: 8–15 mg/m^2 Hydrocortisone: 8–15 mg/m^2 Ara-C: 15–30 mg/m^2	D1, D3, D5

Source: Based on information from Cairo et al. [89]

Table 3.77 COPADM 1 phase of protocol for high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia treatment, of the French Society of Pediatric Oncology LMB86

Drug	Administration	Dose	Days
Vincristine	IV	2 mg/m^2 (maximum dose of vincristine = 2 mg)	D1
MTX at high dose[a]	IV in 4 h	8 g/m^2	D1
Methotrexate	IT	8–15 mg/m^2	D1, D3, and D5
Cytarabine	IT	15–30 mg/m^2	D2, D4, and D6
Hydrocortisone	IT	8–15 mg/m^2	D2, D4, and D6
Doxorubicin	IV	60 mg/m^2	D2
Cyclophosphamide	IV	500 mg/m^2/day (in divided doses of 250 mg/m^2 given two times a day)	D2, 3, and 4
Prednisone	Oral	60 mg/m^2 (in divided doses)	D1 to 5, then reduce over 3 days to 0.

Source: Based on information from Cairo et al. [89]

[a]Start rescue with leucovorin 24 h after starting methotrexate, and give every 6 h until serum methotrexate level is $<1 \times 10^{-7}$ M.

Table 3.78 COPADM 2 phase of protocol for high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia treatment, of the French Society of Pediatric Oncology LMB86

Drug	Administration	Dose	Days
Vincristine	IV	2 mg/m^2 (maximum dose of vincristine = 2 mg)	D1
MTX at high dose[a]	IV in 4 h	8 g/m^2	D1
Methotrexate	IT	8–15 mg/m^2	D1, D3, and D5
Cytarabine	IT	15–30 mg/m^2	D2, D4, and D6
Hydrocortisone	IT	8–15 mg/m^2	D2, D4, and D6
Doxorubicin	IV	60 mg/m^2	D2
Cyclophosphamide	IV	1000 mg/m^2/day (in divided doses of 500 mg/m^2 given two times a day)	D2, 3, and 4
Prednisone	Oral	60 mg/m^2 (in divided doses)	D1 to 5, then reduce over 3 days to 0.

Source: Based on information from Cairo et al. [89]

[a]Start rescue with leucovorin at 24 h after starting methotrexate, and give every 6 h until serum methotrexate level is $<1 \times 10^{-7}$ M.

Table 3.79 Phases CYVE 1 and 2 for CNS-, of protocol for high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia treatment, of the French Society of Pediatric Oncology LMB86

Drug	Administration	Dose	Days
Cytarabine	IV	50 mg/m^2/day	D1 to D5
HD Cytarabine	IV	3000 mg/m^2/day	D2 to D5
Etoposide	IV	200 mg/m^2/day	D2 to D5

Source: Based on information from Cairo et al. [89]

Table 3.80 Phases CYVE 1 and 2 for CNS+, of protocol for high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia treatment, of the French Society of Pediatric Oncology LMB86

Drug	Administration	Dose	Days
Cytarabine	IV	50 mg/m^2/day	D1 to D5
HD Cytarabine	IV	3000 mg/m^2/day	D2 to D5
Etoposide	IV	200 mg/m^2/day	D2 to D5
HD Methotrexate[a]	IV	8000 mg/m^2	D18
Methotrexate and hydrocortisone intrathecally	IT	MTX: 8–15 mg/m^2 Hydrocortisone: 8–15 mg/m^2	D1
Methotrexate, cytarabine, and hydrocortisone intrathecally	IT	MTX: 8–15 mg/m^2 Ara-C: 15–30 mg/m^2 Hydrocortisone: 8–15 mg/m^2	D19

Source: Based on information from Cairo et al. [89]
[a]Start rescue with leucovorin 24 h after starting methotrexate, and give every 6 h until serum methotrexate level is $<1 \times 10^{-7}$ M.

Table 3.81 Phases Mini CYVE 1 and 2 for CNS-, of protocol for high-risk nervous central system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia treatment, of the French Society of Pediatric Oncology LMB86

Drug	Administration	Dose	Days
Cytarabine	IV	50 mg/m^2/day	D1 to D5
Mini HD Cytarabine	IV	2000 mg/m^2/day	D2 to D5
Etoposide	IV	100 mg/m^2/day	D2 to D5

Source: Based on information from Cairo et al. [89]

These Mini CYVE 1 and 2 phases for CNS- are a reduced-intensity therapy dose/schedule of the complete CYVE 1 and 2 for CNS-.

Table 3.82 Phases Mini CYVE 1 and 2 for CNS+, of protocol for high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia treatment, of the French Society of Pediatric Oncology LMB86

Drug	Administration	Dose	Days
Cytarabine	IV	50 mg/m^2/day	D1 to D5
Mini HD Cytarabine	IV	2000 mg/m^2/day	D2 to D5
Etoposide	IV	100 mg/m^2/day	D2 to D5
HD Methotrexate[a]	IV in 4 h	8000 mg/m^2	D18
Methotrexate, cytarabine, and hydrocortisone intrathecally	IT	MTX: 8–15 mg/m^2 Ara-C: 15–30 mg/m^2 Hydrocortisone: 8–15 mg/m^2	D19

Source: Based on information from Cairo et al. [89]
[a]Start rescue with leucovorin 24 h after starting methotrexate, and give every 6 h until serum methotrexate level is $<1 \times 10^{-7}$ M.

These Mini CYVE 1 and 2 phases for CNS+ are a reduced-intensity therapy dose/schedule of the complete CYVE 1 and 2 for CNS+.

Table 3.83 M1 Phase of protocol for high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia treatment, of the French Society of Pediatric Oncology LMB86

Drug	Administration	Dose	Days
Vincristine	IV	2 mg/m^2 (maximum dose = 2 mg)	D1
Methotrexate high dose[a]	IV in 4 h	8 g/m^2	D1
Prednisone	Oral	60 mg/m^2 (divided doses)	D1 to 5, then reduce over 3 days to 0.
Methotrexate, cytarabine, and hydrocortisone	IT	MTX: 8–15 mg Hydrocortisone: 8–15 mg Cytarabine: 15–30 mg	D2
Cyclophosphamide	IV	500 mg/m^2/dose every 12 h	D2 and D3
Doxorubicin	IV	60 mg/m^2	D2

Source: Based on information from Cairo et al. [89]

[a]Start rescue with leucovorin 24 h after starting methotrexate, and give every 6 h until serum methotrexate level is $<1 \times 10^{-7}$ M.

Table 3.84 M2 Phase of protocol for high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia treatment, of the French Society of Pediatric Oncology LMB86

Drug	Administration	Dose	Days
Etoposide	IV	150 mg/m^2/day	D1 to 3
Cytarabine	SC	50 mg/m^2/dose, every 12 h	D1 to 5

Source: Based on information from Cairo et al. [89]

Table 3.85 M3 Phase of protocol for high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia treatment, of the French Society of Pediatric Oncology LMB86

Drug	Administration	Dose	Days
Vincristine	IV	2 mg/m^2 (maximum dose = 2 mg)	D1
Prednisone	Oral	60 mg/m^2/day (in divided doses)	D1 to 5, then reduce over 3 days to 0.
Cyclophosphamide	IV	250 mg/m^2 every 12 h	D1 and 2
Doxorubicin	IV	60 mg/m^2	D1

Source: Based on information from Cairo et al. [89] and Galicier et al. [90]

Table 3.86 M4 Phase of protocol for high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia treatment, of the French Society of Pediatric Oncology LMB86

Drug	Administration	Dose	Days
Cytarabine	SC	50 mg/m^2/dose, every 12 h	D1 to 5
Etoposide	IV	150 mg/m^2/day (in divided doses)	D1 to 3

Source: Based on information from Cairo et al. [89]
M maintenance

3.10 Advanced Burkitt's Lymphoma and ALL L3 – Protocol for Burkitt's Lymphoma of the French Society of Pediatric Oncology (LMB89)

The patients are divided into three groups (A, B, and C), with an ascending treatment intensity scale. The response usually starts after 1 week or after three to four courses of treatment. Group A has a very good prognosis. They are the patients who have suffered complete resection in stage I and abdominal disease in stage II. Patients in Group B are those with stage I not resected, stage II no abdominal involvement, and/or any stage III or IV features. Patients with ALL L3 with involvement of the CNS, with less than 70 % blasts in bone marrow (CNS disease is defined as the presence of blasts in cerebrospinal fluid, in any number, cranial nerve paralysis not related to facial tumor, clinical signs of spinal cord compression or intracranial mass) are accepted in group B; if treatment fails, patients go to group C.

Patients in group C are those with the worst prognosis, as some of these patients have CNS involvement or ALL L3 with at least 70 % blasts in bone marrow [49].

Table 3.87 Classification of risk groups for the protocol for Burkitt's lymphoma treatment of the French Society of Pediatric Oncology (LMB89)

Group	Pre-phase	Induction	Consolidation	Maintenance
A	_	COPAD n°1 COPAD n°2	–	–
B	COP	COPADM n°1 COPADM n°2	CYM n°1 CYM n°2	m1
C	COP	COPADM n°1 COPADM n°2	CYM n°1 CYM n°2	m1 m2 m3 m4 Cranial radiotherapy between m1 and m2 if CNS + (24 Gy).

Source: Based on information from Patte et al. [49]
m maintenance

Table 3.88 Pre-phase (COP) of protocol for Burkitt's lymphoma treatment, of the French Society of Pediatric Oncology (LMB89) (Only groups B and C)

Drug	Administration	Dose	Days
Cyclophosphamide	IV	300 mg/m^2	D1
Vincristine	IV	1 mg/m^2 (maximum dose of vincristine = 2 mg)	D1
Prednisone	IV or Oral	60 mg/m^2/day (divided into two doses per day)	D1 to 7
Methotrexate and hydrocortisone (just group B)	IT	MTX: 15 mg Hydrocortisone: 15 mg	D1
Methotrexate, hydrocortisone, and cytarabine (Group C)	IT	MTX: 15 mg Hydrocortisone: 15 mg Ara-C: 30 mg	D1, D3, D5

Source: Based on information from Patte et al. [49]

Table 3.89 Induction phase (COPADM n°1) of protocol for Burkkit's lymphoma, of the French Society of Pediatric Oncology (LMB89) (Only groups B and C)

Drug	Administration	Dose	Days
Vincristine (Groups B and C)	IV	2 mg/m^2 (maximum dose of vincristine = 2 mg)	D1
Methotrexate at high dose (Groups B and C)	Group B: IV in 3 h Group C: IV in 4 h	Group B: 3 g/m^2 Group C: 8 g/m^2	D1
Folinic acid (Groups B and C)	Oral	15 mg/m^2 every 6 h	D2, 3, and 4
Methotrexate and hydrocortisone (Group B)	IT	MTX: 15 mg Hydrocortisone: 15 mg	D2 and 6
Methotrexate, hydrocortisone, and cytarabine (Group C)	IT	MTX: 15 mg Hydrocortisone: 15 mg Ara-C: 30 mg	D2, 4, and 6
Doxorubicin (Groups B and C)	IV	60 mg/m^2	D2
Cyclophosphamide (Groups B and C)	IV	500 mg/m^2/day (the dose is divided in 250 mg/m^2 and given two times a day)	D2, 3, and 4
Prednisone (Groups B and C)	IV or oral	60 mg/m^2	D1 to 6

Source: Based on information from Patte et al. [49].
Start 1 week after first day of pre-phase [49].

Table 3.90 Induction phase 2 (COPADM n°2) of protocol for Burkitt's lymphoma, of the French Society of Pediatric Oncology (LMB89) (Only groups B and C)

This phase is similar to induction phase COPADM nº1, except for:

Drug	Administration	Dose	Days
Second dose of vincristine	IV	2 mg/m^2 (maximum dose of vincristine = 2 mg)	D6
Change in cyclophosphamide dosage	IV	1 g/m^2/day divided into two doses	D2, 3, and 4

Source: Based on information from Patte et al. [49]

Table 3.91 Induction COPAD phase for risk group A of protocol for Burkitt's lymphoma, of the French Society of Pediatric Oncology (LMB89)

Drug	Administration	Dose	Days
Vincristine	IV	2 mg/m^2 (maximum of 2 mg)	D1 and D6
Doxorubicin	IV	60 mg/m^2	D2
Cyclophosphamide	IV	500 mg/m^2/day, divide the dose and give two times a day	D2, 3, and 4
Prednisone	IV or Oral	60 mg/m^2	D1 to 6

Source: Based on information from Patte et al. [49]

Group A receive two courses of vincristine, doxorubicin, cyclophosphamide, and prednisone.

Table 3.92 Consolidation phase for group B (CYM n ° 1 and 2) of the protocol for Burkitt's lymphoma, of the French Society of Pediatric Oncology (LMB89)

Drug	Administration	Dose	Days
MTX high dose	IV in 3 h	3 g/m^2	D1
Folinic acid	Oral	15 mg/m^2 every 6 h	D2, 3, and 4
Methotrexate and hydrocortisone	IT	MTX: 15 mg Hydrocortisone: 15 mg	D2
Cytarabine	IV in continuous 24-h infusion	100 mg/m^2	D2 to 6
Cytarabine and hydrocortisone	IT	Ara-C: 30 mg Hydrocortisone: 15 mg	D6

Source: Based on information from Patte et al. [49]

Table 3.93 Consolidation phase for group C (CYM n ° 1 and 2) of the protocol for Burkitt's lymphoma, of the French Society of Pediatric Oncology (LMB89)

Drug	Administration	Dose	Days
Cytarabine	IV, continuous 12-h infusion	50 mg/m^2	D1 to 5
Cytarabine high dose	IV in 3 h (to start when Ara-C 50 mg/m^2 finish)	3 g/m^2	D2 to 5
Etoposideo	IV (to start 3 h after finishing Ara-C high-dose)	200 mg/m^2	D2 to 5

Source: Based on information from Patte et al. [49]

Maintenance therapy should be done only for groups B and C [49].

Table 3.94 Maintenance phase 1 (m1) of the Protocol for Burkitt's lymphoma, of the French Society of Pediatric Oncology (LMB89)

Drug	Administration	Dose	Days
Vincristine	IV	2 mg/m^2 (maximum dose = 2 mg)	D1
Methotrexate high dose	Group B: IV in 3 h Group C: IV in 4 h	Group B: 3 g/m^2 Group C: 8 g/m^2	D1
Folinic acid	Oral	15 mg/m^2 every 6 h	D2 to 4
Prednisone	Oral	60 mg/m^2	D1 to 5
Methotrexate and hydrocortisone (only for Group B)	IT	MTX: 15 mg Hydrocortisone: 15 mg	D2
Methotrexate, cytarabine, and hydrocortisone (only for Group C)	IT	MTX: 15 mg Hydrocortisone: 15 mg Cytarabine: 30 mg	D2
Cyclophosphamide	IV	500 mg/m^2	D1 and 2
Doxorubicin	IV	60 mg/m^2	D2

Source: Based on information from Patte et al. [49]

Maintenance should be done in monthly alternated courses [49].

Table 3.95 Maintenance phases 2 and 4 (m2 and m4) of the protocol for Burkitt's lymphoma, of the French Society of Pediatric Oncology (LMB89)

Drug	Administration	Dose	Days
Etoposide	IV	150 mg/m^2	D1 to 3
Cytarabine	SC (divide into two doses)	100 mg/m^2	D1 to 5

Source: Based on information from Patte et al. [49]

Table 3.96 Maintenance phase 3 (m3) of the protocol for Burkitt's lymphoma, of the French Society of Pediatric Oncology (LMB89)

Drug	Administration	Dose	Days
Vincristine	IV	2 mg/m^2 (maximum dose = 2 mg)	D1
Prednisone	Oral	60 mg/m^2	D1 to 5
Cyclophosphamide	IV	500 mg/m^2	D1 and 2
Doxorubicin	IV	60 mg/m^2	D2

Source: Based on information from Patte et al. [49]

3.11 Osteosarcoma

Multiagent chemotherapy prior to and following definitive radical surgery is the standard of care for osteosarcoma treatment. Complete resection of all sites of the disease (including metastatic lesions) is critical for long-term survival [28].

3.11.1 High-Dose Methotrexate (HD MTX) [4]

Table 3.97 Protocol with high-dose methotrexate (HD MTX)

Drug	Administration	Dose	Days
Methotrexate	IV	12 g/m^2/week	One time per week, for 2 to 12 weeks
Folinic acid	IV or Oral	15 mg/m^2 every 6 h	Every 6 h, start 30 h after beginning of MTX, total of ten doses

Source: Based on information from Bragalone [4]

3.11.2 Ifosfamide, Carboplatin, and Etoposide (ICE) (for Malignant Recurrent Solid Tumors) [4]

Repeat this cycle every 21–28 days.

Table 3.98 Protocol with Ifosfamide, carboplatin, and etoposide (ICE)

Medication	Administration	Dose	Days
Ifosfamide	EV	1500 mg/m^2/day	D1, 2, and 3
Carboplatin	EV	300–635 mg/m^2/day	D3
Etoposide	EV	100 mg/m^2/day	D1, 2, and 3
Mesna	EV	500 mg/m^2/dose	Before ifosfamide, 3 h after first dose of mesna, and 3 h after second dose of mesna (total of three doses per day, given every 3 h). Repeat this scheme every day of ifosfamide treatment.

Source: Based on information from Bragalone [4]

3.12 Hepatoblastoma

The German Cooperative Paediatric Liver Tumour Study (HB89) has evaluated the efficacy and toxicity of ifosfamide, cisplatin, and doxorubicin (IPA) in children with resectable and non-resectable hepatoblastoma and has determined the late sequelae, including tubular nephropathy, of tumor treatment. Larger tumors were initially treated with the IPA protocol and resected at second-look surgery. All patients received IPA adjuvantly, after tumor resection. The median follow-up of survivors was 64 months (range, 28–82 months); long-term disease-free survival for stage I was 21 of 21 cases; for stage II, 3 of 6 cases; for stage III, 28 of 38 cases; and for stage IV, 2 of 7 cases; overall disease-free survival was 75 %. Drug resistance developed in 8 of 12 tumors after four or five chemotherapy courses. Acute toxicity was observed in 14 % of IPA courses. Despite a more favourable prognosis in totally fetal and predominantly fetal histologies, the study revealed no relationship between tumor differentiation and response to chemotherapy [113].

In conclusion, IPA chemotherapy, in combination with delayed surgery, was highly effective in the treatment of hepatoblastoma [113].

Table 3.99 Ifosfamide, cisplatin, and doxorubicin (IPA) [4]

Drug	Administration	Dose	Days
Ifosfamide	IV	500 mg/m^2	D1
Ifosfamide	IV in continuous infusion (72 h)	1000 mg/m^2/day	D1 to 3
Cisplatin	IV	20 mg/m^2/day	D4 to 8
Doxorubicin	IV in continuous infusion	30 mg/m^2/day	D9 and 10

Source: Based on information from Bragalone [4] and von Schweinitz et al. [113]

Repeat the cycle every 21 days.

Chapter 4
Background of Drug Interactions

List of tables

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4.1 Basis of Drug Interactions

A drug interaction can change both the pharmacokinetics and the pharmacodynamics of a drug. Changes in pharmacokinetics may modify the absorption, degree of binding to plasma proteins, biotransformation, or excretion of the drug, and more than one alteration can occur concomitantly [6, 52, 53].

Of all hospital admissions in the United States, 2.8 % are for drug interactions and, according to a questionnaire of the American Society of Health-System Pharmacists, drug-drug interactions were classified as one of patient's major concerns in a health service [33].

A multicenter cross-sectional retrospective study, conducted in the intensive care units of seven teaching hospitals in Brazil, analyzed the charts of 1,124 patients admitted in 2007; during 24 h of admission, 793 patients had at least one drug interaction, representing 70.6 % of patients. In total there were 2,299 drug interactions, of 353 types, in which 350

interactions were classified as drug – drug, and 3 as drug – parenteral nutrition, making an average of 2.92 interactions per patient. Of the interactions in the study, 0.1 % represented contraindicated interactions, 36.5 % serious interactions, 50.1 % moderate interactions, and 13.3 % represented low interactions [9].

Most drug interactions that occur in pediatric oncology are related to supportive care and are exacerbated due to individual variations, such as genetics and age [23].

4.1.1 Pharmacokinetic Interactions

- Absorption: Drugs that accelerate gastric emptying tend to increase gastrointestinal absorption, and drugs that delay gastric emptying tend to decrease gastrointestinal absorption. Gastrointestinal motility, splanchnic blood flow, and the drug particle size and pharmaceutical form, as well as physical and chemical factors such as pH, may alter the absorption of drugs [23, 52, 104].
- Distribution: An increase in free drug concentration may be caused by the displacement of the drug of its plasma binding sites or tissues (by a second drug); increased elimination follows, and this reduces the total drug concentration in plasma, resulting that free drug concentration is almost the same as that before the administration of the second drug. Before dynamic equilibrium occurs, however, there may be toxicity due to an increase in the concentration of the free drug. When the second drug that caused the displacement also decreases the elimination of the first drug, there may be high toxicity [23, 54].

The levels of serum albumin (and also the levels of other proteins), if decreased, release drugs to interact with tissues. Albumin production capacity depends on factors such as nutrition. Albumin is synthesized in the liver, and the exposure of hepatocytes to hepatotoxins interferes with this synthesis. Growth hormone, insulin, testosterone, and thyroid

and adrenal cortical hormones influence the amount of albumin production [8, 54, 104].

- Biotransformation: Antineoplastic drugs are mostly metabolized to by-products, which are less liposoluble, and excreted; the liver is the main organ metabolizer of both phase I reactions (oxidation, reduction, or hydrolysis) and phase II reactions (conjugation, methylation, sulfation, acetylation, glucuronidation, or glutathione conjugation). Oxidative metabolism (phase I) usually occurs through the cytochrome P450 enzymatic system, which consists of approximately 100 isoenzymes, such as CYP3A4 (the most abundant enzyme in the liver); CYP3A4 accounts for approximately half of the drug metabolic activities of all cytochrome P450 enzymes [23, 104].

Metabolism by enzymatic induction: Many drugs induce drug-metabolizing enzymes; over 200 drugs cause enzyme induction. Typically, the inducer drug is a substrate for the enzyme, and one of the results of induction is the early elimination of the drug in the body. This may result in no treatment occurring [6, 46].

Metabolism by enzyme inhibition: Enzyme inhibition, especially of the P450 system, decreases the metabolism of drugs metabolized by those enzymes, increasing their effect [5, 54, 104].

Excretion: A drug can change the binding of another drug to plasma proteins, subsequently changing the drug's filtration. Elimination can be altered by the inhibition of tubular secretion, or by alteration on urinary pH, as well as an alteration on urinary flow; both factors may operate at the same time, as well as only one of these factors can be modified [6, 53, 54, 104].

Table 4.1 Pharmacokinetic Interactions

Absorption	Accelerates gastric emptying: Increases gastrointestinal absorption. Delays gastric emptying: Decreases gastrointestinal absorption [23, 54, 104].
Distribution	A drug can displace another drug of its binding site, increasing the concentration of free drug. Later, dynamic equilibrium occurs resulting from the increased elimination, but before that can occur, there may be toxicity due the excess of free drug. If the drug that caused the displacement also decreases the removal of the first drug, there can be high toxicity [23, 54, 104]. The levels of serum albumin and other proteins, if decreased, release the drugs so that they are free to interact with tissues [23, 54, 104].
Biotransformation by enzyme induction	Typically, the inducer is a substrate for the enzyme [23, 104].
Biotransformation by enzyme inhibition	Decreases metabolism, increases the drug's effect [5, 6, 54].
Excretion	Filtration can be altered by a drug that alters the binding of other drug to plasma proteins; tubular secretion may be inhibited; urinary pH, as well as urinary flow, can be changed, or both factors can be modified at the same time [53, 104].

4.1.2 Pharmacodynamic Interactions

Pharmacodynamic interactions are often expected if the mechanism of action of medicines used is taken into account. These interactions occur by several different mechanisms; an

antagonist of a given receptor may decrease the effectiveness of the same receptor agonist. Pharmacodynamics can be changed by competition for the receptor, and can also be changed by another medicine with a mechanism of action in another receptor [6, 52].

Effects of pharmacodynamic interactions: Most drugs are studied in young or middle-aged adults and there is little information on pharmacodynamics and pharmacokinetics in children. Because the pharmacokinetics and pharmacodynamics may be different in children, adjustment of the dose and posological schedule is generally required to achieve the desired therapeutic effect without risk [6].

In childhood, because the disposition of drugs does not vary linearly according to weight or body surface area, there is no trusted formula for calculating a safe and effective dose for children using the adult dose. It must be taken into account that pharmacokinetic variability tends to be higher in periods of physiological change, such as in newborns, premature infants, and individuals at the stage of puberty [6].

- Addition: Drugs used together have additive pharmacological activity, resulting in a sum equal to some of the pharmacological effects of each alone.
- Synergism: This is similar to the additive effect, but the final effect is greater than the sum of the effects of the individual agents.
- Potentialization: This is an increase in the toxicity of an agent when used concomitantly with another non-toxic agent, causing a greater effect of the first agent.
- Antagonism: The agent acts as an antidote to another agent.
- Physiological or Functional Antagonism: The drugs produce opposite effects on the same function.
- Chemical Antagonism: Produces chemical reaction between compounds, inactivating any of them.
- Processing Antagonism: Changes absorption, biotransformation, distribution, or excretion of a drug, thus reducing its effect [6, 52, 54, 105].

Table 4.2 Pharmacodynamic interactions

Additive effect	Sum of the pharmacological activity of single agents [5, 52].
Synergistic effect	Sum of the pharmacological activity of single agents with higher final effect [5, 52].
Potentialization effect	A non-toxic agent enhances the effect of another agent in a toxic interaction [5, 52].
Functional or physiological antagonism	Agents with opposite effects on the same function [5, 52].
Chemical antagonism	Agents react, inactivating any of them [5, 52].
Processing antagonism	Reduction of effect by changing the absorption, biotransformation, distribution, or excretion of a drug [5, 52].

4.2 Drug: Drug Interactions

4.2.1 Drug Interactions (Pharmacokinetics) Involving CYP450

Several P450 enzymes are located in the inner mitochondrial membrane with catalytic sites exposed on the matrix. Another important family of cytochrome P450 enzymes is found in the endoplasmic reticulum of hepatocytes. Many of the substrates of P450 enzymes (in the endoplasmic reticulum) are xenobiotics (compounds synthesized industrially and not found in nature). Through hydroxylation by cytochrome P450 enzymes, hydrophobic compounds become more water soluble and can be excreted by the kidneys. Metabolism by P450 enzymes limits the lifetime of a drug in the bloodstream and thus limits its therapeutic effect [46].

Drug toxicity is also frequently a result of enzymatic conversion, in which the drug molecule is converted into a reactive metabolite [54].

The concomitant administration of CYP450 inducers and chemotherapeutic drugs that are catabolized by cytochrome P450 enzymes may increase the clearance of the chemotherapeutic drug, increasing the risk of relapse and reducing the drug's efficiency; administering these chemotherapy drugs together with CYP450 enzyme inhibitors can decrease clearance and increase toxicity [23].

Competitive inhibition occurs when drugs are substrates of the same CYP isoform; this inhibition is dose-dependent and significant when the isoform is saturated. After discontinuation of the drug that interacts, competitive inhibition is rapidly converted. Non-competitive inhibition occurs when the drug interaction destroys the CYP isoform; after discontinuation of the drug that is interacting, non-competitive inhibition takes days or weeks to be converted, because of the need for new synthesis [23].

Table 4.3 Chemotherapy and enzyme complexes that are substrates with clinical significance

	CYP 2A6	CYP 2B6	CYP 2C8	CYP 2C9	CYP 2C19	CYP 2D6	CYP 2E1	CYP 3A4
Brentuximab								Substrate
Busulfan								Substrate
Cyclophosphamide		Substrate						Substrate
Dacarbazine							Substrate	
Docetaxel								Substrate
Doxorubicin		Inhibitor				Substrate		Substrate
Etoposide								Substrate
Ifosfamide	Substrate				Substrate			Substrate
Imatinib						Inhibitor		Substrate Inhibitor

(continued)

Table 4.3 (continued)

	CYP 2A6	CYP 2B6	CYP 2C8	CYP 2C9	CYP 2C19	CYP 2D6	CYP 2E1	CYP 3A4
Irinotecan		Substrate						Substrate
Lomustine						Substrate		
Paclitaxel			Substrate	Substrate				Substrate
Vinblastine								Substrate
Vincristine								Substrate
Vinorelbine								Substrate

Source: Based on information from Taketomo et al. [59, 60], Bragalone [66], and Beijnen and Schellens [105].

Taking into account that pharmacokinetics and pharmacodynamics would vary more in periods of physiological change, the professionals involved in cancer therapy should be aware of the divergence of enzyme concentrations in these phases. At birth, many drug-metabolizing enzymes are expressed at low concentrations; after birth occurs, specific isoenzymes are induced. CYP2E1 and CYP2D6 appear on the first day after birth; and CYP3A4 and the CYP2C subfamily arise after a week. CYP2A1 is expressed 1–3 months after birth. CYP3A7 is present only in fetal livers. To adjust doses by weight or body surface area, we should take into account that the hepatic metabolism of drugs after the neonatal period is generally faster than in adults. Renal elimination of drugs, in general, is also reduced during the neonatal period, and full-term newborns have pronounced reductions in glomerular filtration rate (2–4 mL/min/1.73 m^2), while premature newborns tend to have further reduced renal function; therefore, the dose regimens of some drugs for newborns must be reduced to avoid the toxic accumulation of drugs. Glomerular filtration rate gradually increases to adult levels (corrected based on body surface area) from ages 8 to 12 months [6].

Table 4.4 Enzymatic conditions to take into account in the choice of therapy and dose adjustment in neonate patients

CYP2E1	Appears on the first day after birth
CYP2D6	Appears on the first day after birth
CYP3A4	Appears 1 week after birth
CYP2C	Appears 1 week after birth
CYP2A1	Appears 1–3 months after birth
Hepatic metabolism	Accelerated after the neonatal period
Renal elimination	Decreased in the neonatal period
Glomerular filtration rate	Decreased in newborns; premature infants have a more decreased glomerular filtration rate. Increases to adult levels (based on adjusted body surface area) from 8 to 12 months

Source: Based on information from Brunton et al. [6]

4.2.2 Drug Interactions (Pharmacokinetics) Involving Binding Proteins and Affinity for Plasma Proteins

These drug interactions are important in oncology, due to the narrow therapeutic index of chemotherapeutic drugs [23].

Plasma proteins make up more than 70 % of plasma solids [47].

Drugs with high affinity for plasma proteins may be displaced by other drugs with a higher affinity for the protein; this may increase the concentration of the free form of the first drug, thereby increasing the toxic effects [23].

α1-Acid glycoprotein (AAG)

AAG is present in plasma at 100 times lower concentrations than albumin. There is evidence that AAG participates in normal coagulation, tissue repair, and immunobiological processes. It is a naturally acid protein, due to the high amount of sialic acid, and it also has a low pKa. Acid and basic drugs can bind to this protein, and it has a site (site I) that binds acid drugs such as warfarin. Basic drugs, such as phenylbutazone, bind in site II. AAG is responsible for the greatest amount of difference in plasma protein binding between individuals. The variability of AAG amounts is vast between healthy and sick patients. AAG contributes significantly to the binding of acid drugs, while the capacity of albumin, or its affinity for binding, is also high for acid drugs.

The binding of basic drugs to AAG is variable because of the variability in the amount of AAG in individuals, also because this protein has high affinity and low capacity on its binding site, and because this protein may be easily saturated by increases in the concentration of the linker drug. Some basic drugs that bind

significantly to AAG and are widely used in children are metoclopramide and prednisolone [55, 104].

Albumin

Albumin is the most important plasma protein and its concentration in healthy individuals does not vary significantly. Albumin is responsible for the major part of the total binding of basic drugs in plasma; propranolol, for example, binds to albumin in an amount of 50 % of this drug present in plasma. Because this protein tends to have low affinity for basic drugs and high capacity for binding to this kind of drug, changes in albumin concentration resulting in marked changes in drug binding are not common; however, significant changes in the amount of plasma albumin may trigger a remarkable change in the binding of albumin to basic drugs. Hyperalbuminemia is rare, but hypoalbuminemia can occur in cases of severe liver disease or severe kidney disease, especially in nephrotic syndrome [55, 104].

4.2.3 Drug Interactions (Pharmacokinetics) Involving Transport Proteins

P-glycoprotein

P-glycoprotein is a carrier protein that is located on the cell membranes of various tissues. P-glycoprotein removes chemical compounds from the cell and carries them, in the circulation, for elimination; it does not metabolize drugs, but carries the drugs to places that expose them to metabolic mechanisms such as the CYP450 system [23].

Table 4.5 Important interactions involving chemotherapy and P-glycoprotein [4, 66]

Drug	P-glycoprotein	Drug interactions
Brentuximab vedotin	Substrate	The effect of brentuximab vedotin can be increased by P-glycoprotein inhibitor drugs. The effect of brentuximab vedotin can be reduced by P-glycoprotein inducer drugs.
Doxorubicin	Substrate/ inducer	The effect of doxorubicin can be increased by P-glycoprotein inhibitor drugs. The effect of doxorubicin can be reduced by P-glycoprotein inducer drugs. Doxorubicin may decrease the effect of P-glycoprotein substrate drugs.
Daunorubicin	Substrate	The effect of daunorubicin can be increased by P-glycoprotein inhibitor drugs. The effect of daunorubicin can be reduced by P-glycoprotein inducer drugs.
Etoposide	Substrate	The effect of etoposide can be increased by P-glycoprotein inhibitor drugs. The effect of etoposide can be reduced by P-glycoprotein inducer drugs.
Idarubicin	Substrate	The effect of idarubicin can be increased by P-glycoprotein inhibitor drugs. The effect of idarubicin can be reduced by P-glycoprotein inducer drugs.

Irinotecan	Substrate	The effect of irinotecan can be increased by P-glycoprotein inhibitor drugs. The effect of irinotecan can be reduced by P-glycoprotein inducer drugs.
Methotrexate	Substrate	The effect of methotrexate can be increased by P-glycoprotein inhibitor drugs. The effect of methotrexate can be reduced by P-glycoprotein inducer drugs.
Paclitaxel	Substrate	The effect of paclitaxel can be increased by P-glycoprotein inhibitor drugs. The effect of paclitaxel can be reduced by P-glycoprotein inducer drugs.
Vincristine	Substrate	The effect of vincristine can be increased by P-glycoprotein inhibitor drugs. The effect of vincristine can be reduced by P-glycoprotein inducer drugs.
Vinblastine	Substrate/ inducer	The effect of vinblastine can be increased by P-glycoprotein inhibitor drugs. The effect of vinblastine can be reduced by P-glycoprotein inducer drugs. Vinblastine may decrease the effect of P-glycoprotein substrate drugs.

Source: Based on information from Bragalone [4, 66].

ATP – Binding Cassettes

ABC transporters are so called because all of them have a domain that binds to ATP (ATP – binding cassettes). They form a large family of multidrug transporters that have two transmembrane domains with six helices and they transport a variety of ions, amino acids, vitamins, steroid hormones, and bile salts through the plasma membrane [48].

The expression of ABC is related to resistance to antineoplastic therapy, changes of antineoplastic drugs, and the toxicity of chemotherapy. Heterogeneity has been described in ABC genes, and some of this heterogeneity are related to changes in the pharmacokinetics and pharmacodynamics of chemotherapeutic drugs. Due to the multiple variations in transporting function and substrates, mutations in the genes and codification of these carriers can contribute to genetic disorders such as cystic fibrosis, neurological disorders, and anemia.

Based on phylogenetic classification, ABC proteins can be divided into seven subfamilies, with designations of ABCA to ABCG [34].

Table 4.6 Relationship between ABC expression and resistance to anticancer therapy

ABC subfamily	Genetic localization	Interaction in chemotherapy or cancer
ABCB1	7p21	Multiple drug resistance; tumor prognostic factor
ABCC1	16p13.1	Multiple drug resistance; tumor prognostic factor
ABCC3	17q21.3	Multiple drug resistance in lung cancer and other cancers
ABCC4	13q32	Transport of analogous nucleoside
ABCC5	3q27	Transport of analogous nucleoside, resistance
ABCC6	16p13.1	Resistance to anthracyclines and epipodophyllotoxins
ABCG2	4q22	Resistance to methotrexate, anthracyclines, topotecan, irinotecan, and mitoxantrone

Source: Based on information from Lockhart et al. [34]

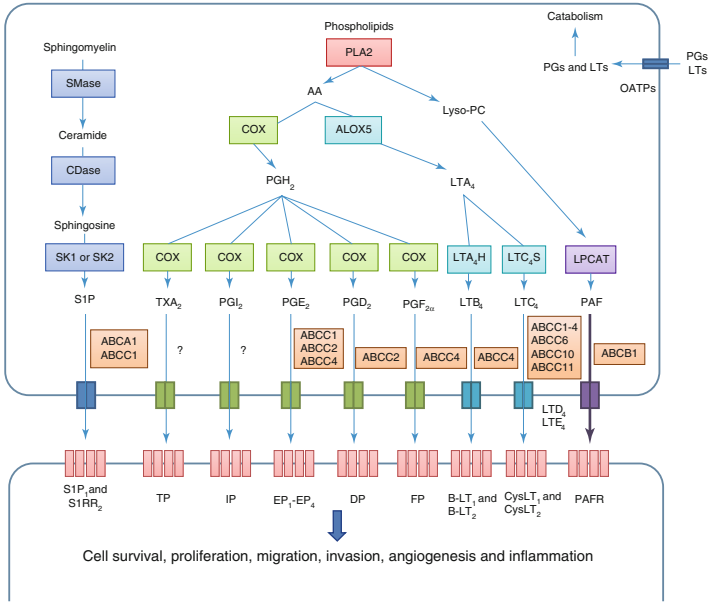

FIG. 4.1 Toxicity linked to ABC family in antineoplastic therapy. *SMase* Sphingomyelinase, *CDase* Ceramidase, *SK1 and SK2* Sphingosine – kinase 1 and 2, *$S1P_1$ and SRR_2* Sphingosine-1-phosphate receptors 1 and 2, *PLA2* Phospholipase A2, *AA* Arachidonic Acid, *Lyso-PC* Lysophosphatidylcholine, *COX* Cyclo-oxygenase, *ALOX5* 5 – lipo – oxygenase, *PGH_2* Prostaglandin H2, *LT* Leukotriene, *LTA_4H* Leukotriene-A4-hydrolase, *LTC_4S* Leukotriene-C4-synthase, *LPCAT* Lysophosphatidylcholine acetyltransferase, *TX* Thromboxane, *PAF* Platelet activating factor, *TP* Thromboxane receptor, *IP* Prostacyclin receptor, *EP_1-EP_4* Prostaglandin E receptors 1-4, *DP* Prostaglandin D2 receptor, *FP* Prostaglandin F receptor, *BLT_1 and BLT_2* Leukotriene B4 receptors 1 and 2, *$CysLT_1$ and $CysLT_2$* Cysteinyl leukotriene receptors 1 and 2, *PAFR* Receptor of platelet activating factor (Source: Based on information from Fletcher et al. [20])

4.3 Beneficial Drug Interactions in Clinical Protocols

4.3.1 Methotrexate and Leucovorin

Leucovorin is used in conjunction with methotrexate in protocols to decrease what has been determined as the greatest

effect of methotrexate: depletion of intracellular folate, which is a consequence of the inhibition of the enzyme dihydrofolate reductase [50].

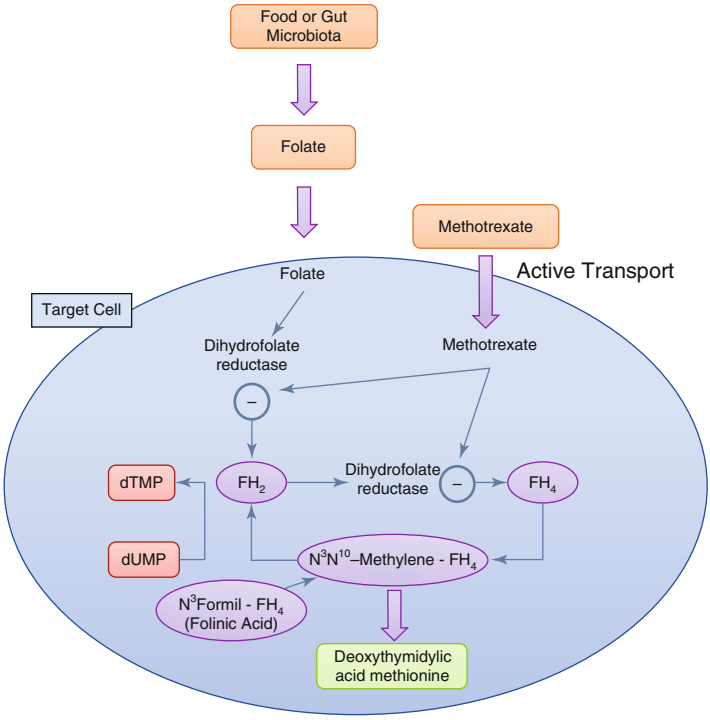

FIG. 4.2 Mechanism of action of leucovorin (folinic acid). *dTMP* deoxythymidine monophosphate, *dUMP* deoxyuridine monophosphate (Source: Based on information from Harvey and Mycek [25])

The conversion of deoxyuridine monophosphato (dUMP) to deoxythymidine monophosphato (dTMP) requires methylene-tetrahydrofolate. Folate pool repletion is exerted by dihydrofolate reductase; methotrexate inhibits this enzyme, inhibiting DNA synthesis, because there is no dUMP conver-

sion to dTMP; this block is responsible for the cytotoxic effects of methotrexate [30].

This is a pharmacodynamic interaction [23].

4.3.2 Doxorubicin and Dexrazoxane

Dexrazoxane is used to decrease the cardiotoxicity of doxorubicin, reducing the risk of cardiomyopathy in children. It is widely used, and there are already leaflet results of studies in children; it is used at a ratio of 10: 1 (dexrazoxane at 10 times the dose of doxorubicin) in children. Dexrazoxane crosses cell membranes, is hydrolysed inside the cardiac muscle fiber, and becomes a chelating agent with an open ring, able to bind to metal ions, inhibiting the oxidative stress caused by free radicals generated by iron ions in the formation of an iron-doxorubicin complex and the subsequent release of the free radicals in heart muscle [13].

Anthracyclines (such as doxorubicin) enter cardiomyocytes by passive diffusion, stimulating free radical production, damaging the cell, and also inducing toxic damage to the mitochondria of the cardiomyocytes. Several mitochondrial enzymes, such as nicotinamide adenine dinucleotide (NADH) dehydrogenase, cytochrome P-450 reductase, and xanthine oxidase, are involved in generating free oxygen radicals. Another toxic mechanism of doxorubicin is the increase of superoxide formation, produced by increasing endothelial nitric oxide synthase, promoting intracellular hydrogen peroxide formation [24, 108].

In doxorubicin cardiomyopathy, all four cardiac chambers may be dilated, although severe dilatations of ventricles and atria are less common than in ischemic and non-ischemic dilated cardiomyopathies. The ventricular ejection fraction, and also contractile function, is reduced. There is concomitant diastolic dysfunction. Doxorubicin can also produce significant injury to non-cardiac muscle, as the characteristic pattern of doxorubicin-related damage to the heart, and the degree of myocyte damage is apparently dependent upon the doxorubicin concentration in the tissue [44, 108, 109].

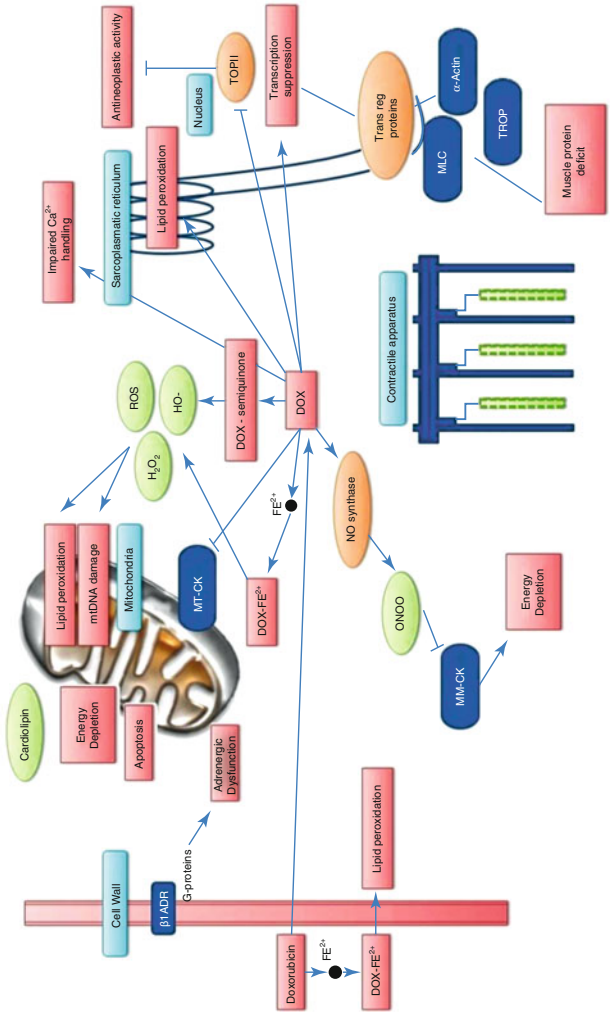

FIG. 4.3 Mechanism of doxorubicin cardiotoxicity. *β1ADR* Adrenergic β1 receptor, *mtDNA* Mitochondrial deoxyribonucleic acid, *ROS* Reactive oxygen species, *MT-CK* Mitochondrial creatine kinase, *DOX* Doxorubicin, *DOX-Fe*$^{2+}$ Doxorubicin with Fe^{2+} complex, *TOPII* Topoisomerase II, *MM-CK* Muscle creatine kinase, *MLC* Myosin light chain, *TROP* Troponin, *Trans reg proteins* Transcriptional regulatory proteins (Source: Based on information from Lipshultz et al. [14])

4.3.3 *Ifosfamide and Mesna or Cyclophosphamide and Mesna*

Mesna is used to prevent hemorrhagic cystitis in patients receiving therapy with high doses of ifosfamide or high doses of cyclophosphamide. Mesna is oxidized to dimesna in blood, and dimesna is reduced to mesna in the kidneys. A free thiol group in mesna binds to and inactivates acrolein, which is the urotoxic metabolite of ifosfamide and cyclophosphamide [4].

Ifosfamide is a prodrug activated by hepatic cytochrome P450 isoform catalysis. Ifosfamide can course two oxidation pathways; one leads to the active metabolite isophosphoramide mustard, but both pathways form toxic metabolites. The detoxification pathway produces chloroacetaldehyde; the 4 – hydroxylation pathway results in acrolein and also in the activation of ifosfamide mustard. The 4 – hydroxy – ifosfamide is converted into its aldophosphamide tautomer, which is also subject to inverse conversion. The aldoifosfamide division involve detoxification — mediated by aldehyde dehydrogenase 1A1 to form the inactive metabolite carboxy – ifosfamide — and non-enzymatic elimination [3, 61].

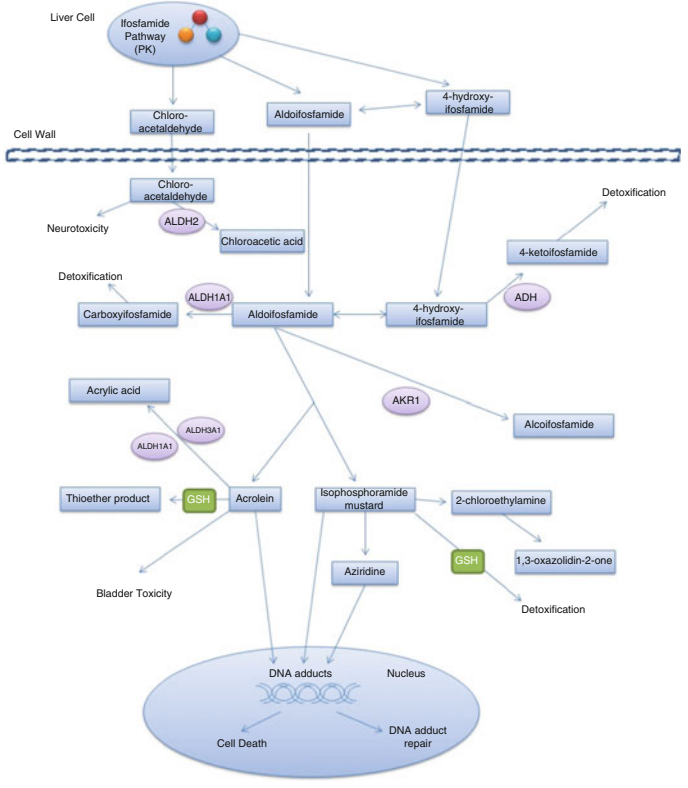

FIG. 4.4 Mechanism of ifosfamide toxicity. *PK* Pharmacokinetics, *ALDH* Aldehyde dehydrogenase, *ADH* Antidiuretic hormone, *AKR1* Aldo-Keto Reductase 1, *GSH* Glutathione (Source: Based on information from Lowenberg et al. [3])

4.3.4 Methotrexate and Sodium Bicarbonate

Basic drugs are better excreted in patients with acid urinary pH, while acid drugs are better excreted in alkaline urinary pH [46].

Methotrexate is an acid drug; thus, it is better excreted in alkaline pH urine. Delayed drug clearance is one of the major factors responsible for drug toxicity. The excretion of methotrexate is primarily in the kidney; if urine pH is less than 6, this acid drug tends to precipitate. Because there is a possibility of acid drugs precipitation, alkalinization of the urine and hydration are recommended. Hydration and urine alkalinization with sodium bicarbonate are also recommended in cases of intoxication, to prevent the precipitation of methotrexate and its metabolites in the renal tubules [38, 104].

4.4 Drug Interactions Involving Prodrugs

Prodrugs require enzymatic degradation to become the active form [52, 105].

Cyclophosphamide and mercaptopurine are prodrugs, having opposite effects on metabolic inhibition and activation, and the time required to induce or inhibit CYP450 is important [23, 105].

Irinotecan is a prodrug that is biologically activated by plasmatic and intracellular carboxylesterases, thus being transformed into a potent inhibitor of topoisomerase. The carboxylesterases are part of a superfamily of hydrolytic enzymes that catalyze the hydrolysis of ester and amide compounds; these enzymes are located in the endoplasmic reticulum and cytosol of some cell types and are involved in both the activation of certain prodrugs and in detoxification, because the deactivation of potentially toxic products generated by CYP is done by hydrolytic enzymes [5, 6].

4.5 Anticonvulsants and Antineoplastic Drugs

Carbamazepine, phenobarbital, phenytoin, and valproic acid are inducers or inhibitors of CYP450, leading to complications in the concomitant treatment with chemotherapy drugs that are metabolized by CYP450 and these anticonvulsants, manifested as reduction of the effectiveness of chemotherapy or increased toxicity [23].

Phenytoin and phenobarbital are known to induce liver enzymes and to be involved in many significant adverse interactions [37].

Phenytoin is a strong inducer of CYP3A4, 2B6, 2C8, 2C9, and 2C19; while phenobarbital strongly induces CYP3A4, 1A2, 2A6, 2B6, 2C8, and 2C9 [60], as well as inducing CYP2C9 and CYP1A6 enzymes [23].

The concomitant administration of cyclophosphamide and phenobarbital in mice showed a reduction of 26 % in phosphoramide mustard, which is the active metabolite of cyclophosphamide; this interaction can summarize that of all the barbiturates, and all of them are activators of enzymes. Phenytoin may reduce the effectiveness of chemotherapy drugs that are metabolized extensively in the liver. The concomitant administration of irinotecan and phenytoin may cause a decrease in systemic exposure to irinotecan and SN-38 (the active metabolite of irinotecan). It has been established that there is an increase in the clearance of etoposide if it is administered concomitantly with phenytoin or phenobarbital [23].

These interactions between anticonvulsants and antineoplastic drugs are pharmacokinetic interactions, involving CYP450 enzymes [23, 105].

4.6 Drug Interactions Involving Anti-inflammatory and Antineoplastic Drugs

4.6.1 Drug Interactions Involving Imatinib and Nonsteroidal Anti-inflammatory Drugs

Patients with chronic myeloid leukemia frequently make use of nonsteroidal anti-inflammatory drugs for treating musculoskeletal complaints, such as muscle cramps, myalgia, and arthralgia. Some studies have suggested that the transporter responsible for the renal uptake and secretion of nonsteroidal anti-inflammatories is the organic anion transporter-1 (OAT-1); despite this, the organic cation transporter-1 (OCT-1) is the primary active protein for imatinib uptake into BCR-ABL-positive cells. Diclofenac and ibuprofen resulted in significant changes in OCT-1 activity, kinase inhibition, and imatinib efficacy *in vitro*; in therapy, diclofenac seems to improve the effect of imatinib without adding greatly to the toxicity, while, in contrast, ibuprofen seems to reduce the effect of imatinib; thus, the concomitant use of nonsteroidal anti-inflammatory drugs with imatinib should be monitored [69].

4.6.2 Drug Interactions Involving Methotrexate and Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs should not be administered with high doses of methotrexate, because this may increase and prolong the serum level of methotrexate. The methotrexate doses used for psoriasis can lead to unexpected toxicities. Caution should be exercised in the use of salicylates and nonsteroidal anti-inflammatory drugs with low doses of methotrexate [4, 103].

This kind of interaction is due to the characteristic of acidic drugs, such as methotrexate, that they are best excreted in alkaline urine; therefore, if the patient makes use of salicylates, for example, the pH of the urine will become more acid, hindering the excretion and increasing the toxicity of acid drugs such as methotrexate [52].

4.6.3 Anti-inflammatory Drugs That Inhibit or Induce Enzyme Complexes

A wide range of anti-inflammatories is used in pediatric oncology practice, although there are no data about some anti-inflammatories regarding which enzymes or specific proteins they can bind, inhibit, or induce. The majority of potential drug interactions seem to have minor clinical relevance, and when the anti-inflammatories are enzyme inhibitors or inducers, they are weak or moderate inhibitors/inducers in most cases. The potential for interactions with significant clinical relevance involving antineoplastic drugs and anti-inflammatory drugs is mostly due to the acid characteristic of nonsteroidal anti-inflammatories (described in the section 'Drug Interactions Involving Methotrexate and Nonsteroidal Anti-Inflammatory Drugs'). There is also potential for interaction with dexamethasone, which has the ability to modulate P-glycoprotein and is a strong inducer of CYP; the interactions involving dexamethasone are described in the 'Antineoplastic and Antiemetic Drugs' section [4, 23, 31, 52, 59].

Table 4.7 Nonsteroidal anti-inflammatory drugs and enzyme complexes that they inhibit or induce

	CYP 1A2	CYP 2B6	CYP 2C8	CYP 2C9	CYP 2C19	CYP 2D6	CYP 2E1	CYP 3A4
Aspirin				Substrate (With minor clinically relevant drug interaction potential)	Inducer (Weak to moderate)			
Diclofenac	Substrate (With minor clinically relevant drug interaction potential) Inhibitor (Weak)	Substrate (With minor clinically relevant drug interaction potential)	Substrate (With minor clinically relevant drug interaction potential)	Substrate (With minor clinically relevant drug interaction potential) Inhibitor (Weak)	Substrate (With minor clinically relevant drug interaction potential)	Substrate (With minor clinically relevant drug interaction potential)	Inhibitor (Weak)	Substrate (With minor clinically relevant drug interaction potential) Inhibitor (Weak)

(continued)

Table 4.7 (continued)

	CYP 1A2	CYP 2B6	CYP 2C8	CYP 2C9	CYP 2C19	CYP 2D6	CYP 2E1	CYP 3A4
Ibuprofen				Substrate (With minor clinically relevant drug interaction potential) Inhibitor (Weak)	Substrate (With minor clinically relevant drug interaction potential)			
Meloxicam				Inhibitor (Weak)				Substrate (With minor clinically relevant drug interaction potential)

Source: Based on information from Taketomo et al. [59]

Table 4.8 Steroidal anti-inflammatories and enzyme complexes/proteins for which they are substrates, or which they inhibit or induce

	CYP 2A6	CYP 2B6	CYP 2C9	CYP 2C19	CYP 3A4	P-glycoprotein
Dexamethasone	Inducer (Weak to moderate)	Inducer (Weak to moderate)	Inducer (Weak to moderate)		Substrate (With minor clinically relevant drug interaction potential) Inducer (Strong)	Substrate Inhibitor Inducer
Hydrocortisone					Substrate (With minor clinically relevant drug interaction potential) Inducer (Weak to moderate)	Substrate

(continued)

Table 4.8 (continued)

	CYP 2A6	CYP 2B6	CYP 2C9	CYP 2C19	CYP 3A4	P-glycoprotein
Prednisolone					Substrate (With minor clinically relevant drug interaction potential) Inhibitor (Weak)	
Prednisone				Inducer (Weak to moderate)	Substrate (With minor clinically relevant drug interaction potential) Inducer (Weak to moderate)	

Source: Based on information from Taketomo et al. [59]

4.7 Drug Interactions Involving Drugs for Pain Management and Antineoplastic Drugs

In pediatric patients many drugs are used for the management of pain during all therapy, including the extensive use of narcotics and opioids, which is discussed in this section. Drug interactions involving non-opioid analgesics are discussed in the '*Drug Interactions Involving Methotrexate and Nonsteroidal Anti-inflammatory Drugs*' section.

There are some important interactions between antineoplastic drugs and opioid or narcotic drugs, and they need to be taken into account to choose the best medication for pain management. Methadone may increase the levels and effects of doxorubicin, by moderately inhibiting CYP2D6, for which doxorubicin is a substrate; anesthetic drugs may be used concomitantly with chemotherapy with caution, as it has been shown that procaine increases the toxic effect of doxorubicin. From the viewpoint of interactions with antineoplastic drugs, morphine is quite safe, and does not induce or inhibit enzymes with clinical relevance; however, for both morphina and liposomal morphine, studies of drug interactions with peginterferon alfa-2b showed a decreased effect of morphine in this association. P-glycoprotein or ABCB1 inducers can also reduce the effect of both presentations of morphine; P-glycoprotein or ABCB1 inhibitors can increase the effect of morphine. Tramadol should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors, due to the risk of seizures and serotonin syndrome; the effect of tramadol can be decreased by 5HT3 antagonists, by moderate or strong CYP2D6 inhibitors (like imatinib), and by strong CYP3A4 inducers (like dexamethasone), and can be increased by moderate or strong CYP3A4 inhibitors (like imatinib) [59, 103, 104, 107].

4.8 Antineoplastic and Antiemetic Drugs

4.8.1 Aprepitant

Aprepitant is a potent and selective antagonist of substance P; this drug acts on the neurokinin 1 (NK1) receptor and is used in pediatric oncology in combination with other antiemetic drugs, such as ondansetron and dexamethasone, despite there being a paucity of studies about its safety and efficacy in childhood [22, 106].

Aprepitant has a limited use in pediatric oncology also due to its ability to interact with chemotherapeutic drugs and because there are few studies about the dosage used in pediatrics. Aprepitant is substrate and inhibitor of CYP3A4 and may also inhibit CYP2C9, 2C8, and 2C19. As many chemotherapeutic drugs are metabolized by CYP3A4, there is a risk of increased toxic effects of chemotherapy with aprepitant [23, 106].

There is an important interaction in pediatric oncology, of aprepitant with dexamethasone, in which the dose of dexamethasone should be reduced by approximately 50 % in children under 18 years, if given either tablet of 125 or 80 mg of aprepitant, according to studies with patients between 12 and 18 years old, using 125 mg or 80 mg of aprepitant with dexamethasone. The recommendation to reduce the dexamethasone dose in 50% is done only to pediatric patients [22].

Table 4.9 Drug interactions involving aprepitant and dexamethasone

Drug	Associated drug	Result of interaction
Aprepitant	Dexamethasone	Increase in area under the curve (AUC) of dexamethasone; should reduce dexamethasone dose by 50 %.

Source: Based on information from Haidar and Jeha [23].

Table 4.10 Drug interactions involving aprepitant and chemotherapy

Drug	CYP 3A4	CYP 2C8	CYP 2C9	Interaction with aprepitant
Cyclophosphamide	Substrate [60]			Aprepitant may increase the toxicity of chemotherapy, by enzymatic inhibition and reduction of cyclophosphamide metabolism [23].
Docetaxel	Substrate [60]			Aprepitant may increase the toxicity of chemotherapy, by enzymatic inhibition and reduction of docetaxel metabolism[23].
Doxorubicin	Substrate [60]			Aprepitant may increase the toxicity of chemotherapy, by enzymatic inhibition and reduction of doxorubicin metabolism[23].
Etoposide	Substrate [60]			Aprepitant may increase the toxicity of chemotherapy, by enzymatic inhibition and reduction of etoposide metabolism [23].
Ifosfamide	Substrate [60]			Aprepitant may increase the toxicity of chemotherapy, by enzymatic inhibition and reduction of ifosfamide metabolism [23].

(continued)

Table 4.10 (continued)

Drug	CYP 3A4	CYP 2C8	CYP 2C9	Interaction with aprepitant
Irinotecan	Substrate [60]			Aprepitant may increase the toxicity of chemotherapy, by enzymatic inhibition and reduction of irinotecan metabolism[23].
Paclitaxel	Substrate [60]	Substrate [60]	Substrate [60]	Aprepitant may increase the toxicity of chemotherapy, by enzymatic inhibition and reduction of paclitaxel metabolism [23].
Vinblastine	Substrate [60]			Aprepitant may increase the toxicity of chemotherapy, by enzymatic inhibition and reduction of vinblastine metabolism [23]
Vincristine	Substrate [60]			Aprepitant may increase the toxicity of chemotherapy, by enzymatic inhibition and reduction of vincristine metabolism [23].
Vinorelbine	Substrate [60]			Aprepitant may increase the toxicity of chemotherapy, by enzymatic inhibition and reduction of vinorelbine metabolism [23].

4.8.2 Dexamethasone and Chemotherapy

Dexamethasone is used for preventing nausea and vomiting in patients in whom anticancer therapies with high emetogenic potential are used. Studies have shown a significant increase in the area under the curve (AUC) of dexamethasone when combined with an aprepitant; the American Society of Clinical Oncology (ASCO) recommends reducing the dexamethasone dose to half in these cases associated with aprepitant use (table 4.9) [23].

Dexamethasone may increase the clearance of chemotherapeutic drugs that are substrates of CYP3A4 and P-glycoprotein, by the induction of CYP3A4 and the modulation of P-glycoprotein [23, 31, 104].

Table 4.11 Drug interactions involving dexamethasone and chemotherapy

Drug	CYP3A4	P-Glycoprotein	Interaction with dexamethasone
Cyclophosphamide	Substrate [60]	–	Increased clearance of chemotherapy drug, reduced effect [23].
Docetaxel	Substrate [60]	Substrate [60]	Increased clearance of chemotherapy drug, reduced effect [23].
Daunorubicin	–	Substrate [60]	Increased clearance of chemotherapy drug, reduced effect [23].
Doxorubicin	Substrate [60]	Substrate/Inducer [60]	Increased clearance of chemotherapy drug, reduced effect [23].
Etoposide	Substrate [60]	Substrate [60]	Increased clearance of chemotherapy drug, reduced effect [23].
Idarubicin	–	Substrate [60]	Increased clearance of chemotherapy drug, reduced effect [23].
Ifosfamide	Substrate [60]	–	Increased clearance of chemotherapy drug, reduced effect [23]. The interaction appears to have minimal clinical significance, because there was no evidence of change in the AUC of 4-hydroxy-ifosfamide [31].

Irinotecan	Substrate [60]	Substrate [60]	Increased clearance of chemotherapy drug, reduced effect [23]. Important clinically significant effect; the effects can last for 3 weeks after discontinuation of dexamethasone. Avoid concomitant use, otherwise consider increasing the irinotecan dose according to protocols and clinical indications [31].
Paclitaxel	Substrate [60]	Substrate [60]	Increased clearance of chemotherapy drug, reduced effect [23]. Monitor clinical efficacy [31].
Vincristine	Substrate [60]	Substrate [60]	Increased clearance of chemotherapy drug, reduced effect [23]. Monitor clinical efficacy [31].
Vinblastine	Substrate [60]	Substrate/Inducer [60]	Increased clearance of chemotherapy drug, reduced effect [23]. Monitor clinical efficacy [31].
Vinorelbine	Substrate [60]	–	Increased clearance of chemotherapy drug, reduced effect [23]. Monitor clinical efficacy [31].

4.9 Antacids and Chemotherapy

Proton pump inhibitors, such as omeprazole, are widely used in children with cancer for the treatment and prevention of esophageal reflux and gastritis. Omeprazole may delay the elimination of high doses of methotrexate, probably by competition with efflux proteins; omeprazole can be replaced by sucralfate or by a histamine type 2 receptor blocker [23].

There are reports that imatinib can cause stomach upset, so antacids are widely administered concomitantly with imatinib. Antacids, by increasing the pH of the stomach, can slow gastric emptying and also antagonize ATP – binding cassette transporters, which may reduce the absorption of imatinib [16, 110].

Table 4.12 Drug interactions involving antacids and chemotherapy

Antacid	Antineoplastic drug	Interaction	Observation
Proton pump inhibitors, such as omeprazole	Methotrexate [23, 104]	Omeprazole may delay the elimination of high doses of methotrexate, probably by competition with efflux protein [23, 104].	Omeprazole can be replaced by sucralfate or by a histamine receptor-2 blocker [23].
All antacids	Imatinib [16]	Antacids, because they increase the pH of the stomach, may delay gastric emptying and also antagonize ATP – binding cassette transporters, which can reduce the absorption of imatinib. [16]	

4.10 Antineoplastic Agents and Antimicrobial Agents

4.10.1 Macrolide Antibiotics

Vinblastine, vincristine, and vinorelbine interact with clarithromycin and erythromycin by the inhibition of the anticancer drug's metabolism, by the inhibition of CYP3A4, and by the inhibition of P-glycoprotein efflux with vinblastine. Due to such interactions, the choice of another anticancer agent must be considered, or complete blood counts must be done; attention must be paid to signs of toxicity, such as pain, numbness, jaw pain, abdominal pain, constipation, and paralytic ileus [32].

Clarithromycin and erythromycin may increase the risk of poisoning by busulfan (manifested by findings such as pulmonary fibrosis and veno-occlusive disease) by increasing plasma concentrations of busulfan, due to the 25 % decreased clearance of busulfan caused by macrolides, and due to these macrolides increasing the AUC of busulfan [32].

If the administration of a macrolide antibiotic is required, the best option is azithromycin, as it is less likely that this macrolide will have unfavorable interactions when used with chemotherapy drugs [23].

4.10.2 Aminoglycoside Antibiotics

It is well established that aminoglycosides (such as amikacin and gentamicin) can cause ototoxicity and dose-dependent nephrotoxicity; the reduced hearing may be severe and irreversible in predisposed individuals [2].

Aminoglycosides associated with platinum compounds may increase the risk of nephrotoxicity and renal failure, as well the risk of ototoxicity, due to the additive toxic effects [32].

4.10.3 Antimicrobials for Tuberculosis and Chemotherapy Drugs

Rifampicin induces CYP3A4 and may decrease the therapeutic response of chemotherapy drugs that are metabolized by this enzyme complex. It is recommended to monitor the clinical efficacy of vincristine and vinblastine when used with rifampicin and to evaluate increased doses of these agents, also monitor according to the clinical indications [32].

Isoniazid is a strong inhibitor of CYP3A4 and CYP2C9 and a weaker inhibitor of 2C19, unlike rifampicin; rifampicin induces CYP450 enzymes as well as P-glycoprotein [23, 60].

4.10.4 Ceftriaxone and Platinum Compounds

The interaction of ceftriaxone and platinum derivative antineoplastic drugs has a toxic additive effect, caused by this antimicrobial being nephrotoxic and the added effect of nephrotoxic chemotherapy; concomitant use of these drugs should be undertaken with caution [21].

4.10.5 Vancomycin and Platinum Compounds

Vancomycin in association with platinum compounds may increase the risk of nephrotoxicity and renal failure, due to toxic additive effects [32].

4.10.6 Antineoplastic Drugs and Antibiotics Derived from Penicillin

Penicillin inhibits the proximal tubular secretion of methotrexate, increasing its effect and resulting in severe toxic renal, hepatic, and hematological effects, especially at higher

doses of this antineoplastic drug; the interaction may cause myelosuppression and mucositis even at low doses of methotrexate. Substitution with an antibiotic not derived from penicillin should be considered [32].

4.10.7 Sulfamethoxazole and Trimethoprim With Methotrexate

The effect of the interaction between sulfamethoxazole/trimethoprim and methotrexate is an increased plasma concentration of methotrexate, resulting in toxic effects such as myelosuppression, liver cirrhosis, and pulmonary toxicity [32].

Both trimethoprim and methotrexate block the reinduction of dihydrofolate in tetrahydrofolate by the inhibition of dihydrofolate reductase, resulting in an additive effect. Sulfamethoxazole, as seen with all sulfa drugs, can release methotrexate from plasma proteins, and can also inhibit the renal tubular secretion of methotrexate [23].

Table 4.13 Drug interactions involving antibiotic drugs and chemotherapy drugs

Drug	Enzyme complex/ protein, or cause of the interaction	Drug that interacts	Interaction	Observation
Macrolide Antibiotics	Inhibition of CYP3A4 and P-glycoprotein [32].	Vinblastine, vincristine, and vinorelbine [32].	Inhibition of antineoplastic drug metabolism and efflux of vinblastine with P-glycoprotein [32].	Due to the interaction, consider choosing another antineoplastic agent, or monitor complete blood count and pay attention to signs of toxicity, such as pain, paresthesia, jaw pain, abdominal pain, intestinal constipation, and paralytic ileus [32].
Macrolide Antibiotics	Inhibition of CYP3A4 and P-glycoprotein [32].	Busulfan [32]	May increase the risk of intoxication by busulfan (such as pulmonary fibrosis and veno-occlusive disease) by increasing plasma concentrations of busulfan, due to the 25 % decreased clearance of busulfan caused by macrolides, and also due to the increase in the AUC of busulfan [32].	If the administration of a macrolide antibiotic is required, the best option is azithromycin, because, of the macrolide drugs, it is less likely to cause unfavorable interactions when used with chemotherapy [23].

(continued)

Table 4.13 (continued)

Drug	Enzyme complex/protein, or cause of the interaction	Drug that interacts	Interaction	Observation
Aminoglycoside Antibiotics	Ototoxicity and nephrotoxicity; dose-dependent; reduction in hearing can be severe and irreversible in predisposed individuals [2].	Platinum compounds [32]	Aminoglycosides associated with platinum compounds may increase the risk of nephrotoxicity and renal failure, as well ototoxicity, due to the toxic additive effect [32].	
Ceftriaxone	Nephrotoxicity [21].	Platinum compounds [21, 23]	Additive nephrotoxic effect [21, 23].	Concomitant use should be undertaken with caution [21].
Rifampicin	Induction of CYP3A4, 2C9, and 2C19, in addition to P-glycoprotein [23, 32].	Vinca alkaloids [32]	Decreased effect of chemotherapy through inhibition of CYP3A4 [32].	Monitor clinical efficacy and evaluate increases in vincristine and vinblastine doses, also monitor according to the indications [32].

Isoniazid	Strong inhibition of CYP3A4, CYP2C9, and 2C19 [23].	Vinca alkaloids [60]	Increases the effect and toxicity of chemotherapy by decreasing enzymatic metabolism [40].	
Vancomycin	Nephrotoxicity [32].	Platinum compounds [60]	Increases the risk of nephrotoxicity and renal failure due to toxic additive effects [32].	
Antibiotics derived from penicilin	Penicillin inhibits the proximal tubular secretion of methotrexate [23].	Methotrexate [23]	Potentialization of the effect of methotrexate, by inhibition of proximal tubular secretion. This results in severe toxic renal, hepatic, and hematological effects, especially with high doses of the antineoplastic drug; this interaction may cause myelosuppression and mucositis even at low doses of methotrexate [23].	Consider substituting with an antimicrobial not derived from penicillin [23].

(continued)

Table 4.13 (continued)

Drug	Enzyme complex/protein, or cause of the interaction	Drug that interacts	Interaction	Observation
Sulfamethoxazole with trimethoprim	Blocking of reinduction of dihydrofolate to tetrahydrofolate by inhibition of dihydrofolate reductase, causing the release of methotrexate from plasma proteins and inhibition of the renal tubular secretion of methotrexate [23].	Methotrexate [32]	Increased methotrexate concentrations in plasma, leading to toxic effects, such as myelosuppression, liver cirrhosis, and pulmonary toxicity [32]. Both trimethoprim and methotrexate block reinduction of dihydrofolate to tetrahydrofolate by inhibition of dihydrofolate reductase, resulting in an additive effect. Sulfamethoxazole, as with all sulfa drugs, can release methotrexate from plasma proteins, and can also inhibit the renal tubular excretion of methotrexate [23].	

4.11 Antineoplastic Drugs and Antifungals

4.11.1 Amphotericin B

Amphotericin B is nephrotoxic and should not be combined with other nephrotoxic drugs such as cisplatin and methotrexate in high doses. Studies have demonstrated that the combination was lethal in mice with glioma; they had hematuria within 24 h [23].

4.11.2 Azole Antifungals

Voriconazole has a surprisingly broad spectrum of action, but it is a drug whose pharmacokinetics have not been clearly elucidated. In children over age 12 years, which is usually the age above which patients are selected for studies, voriconazole tended to show non-linear pharmacokinetics with the use of doses established in specific schemes. For adults it has been proposed that the dose be based on serum concentration, but the ideal serum concentration remains uncertain; some of the individual variability in the pharmacokinetics of voriconazole is due to polymorphisms in the gene that encodes CYP2C19, generating an increase or decrease in the metabolism of voriconazole. In children, the question of the pharmacokinetics of voriconazole is more critical than in adults, and the optimal dose for prophylaxis in children aged between 2 and 12 years seems to be 7 mg/kg, two times a day; in children under 2 years old, the optimal dose seems to be 8.5 mg/kg, two times a day. It has been established from research that, for children under 12 years of age and for children aged from 12 to 14 years weighing less than 50 kg, the maintenance dose is 8 mg/kg, two times daily, but there is no acceptable universal standard [15].

Voriconazole is a substrate (high) of CYP2CP , is also a substrat of CYP2C19, and a low substrate of 2A4; it is a moderate inhibitor of CYP2C9 and 3A4 and a weak inhibitor of

2C19. It has broad interactions with drugs used in anticancer therapy, including support drugs. Proton pump inhibitors increase levels of voriconazole. Voriconazole increases the serum levels and toxicity of corticosteroids, vincristine, imatinib, and irinotecan. Voriconazole may increase, by 1.7 to 3 times, the concentration of cyclosporine and tacrolimus. The cyclosporine dose should be reduced by 50 % and that of tacrolimus should be reduced by 66 % of its normal dose when used with voriconazole. Researchers have found that, when used with voriconazole, sirolimus must be reduced by 90 % of the original dose, but concomitant use remains contraindicated [15, 107].

Azole antifungals used in conjunction with vinca alkaloids can cause neurotoxicity; it is recommended to stop the use of the antifungal 24 h before chemotherapy and return after 24 h; if this is not possible, use an antifungal from the class of echinocandins (e.g., micafungin or caspofungin) [23, 111].

Table 4.14 Drug interactions involving antifungals and antineoplastic drugs

Drug	Enzyme complex, protein, or cause of interaction	Drug that interacts	Interaction	Clinical action
Amphotericin B	Nephrotoxic drug [23]	Nephrotoxic drugs such as cisplatin and methotrexate in high doses [23]	Lethal in mice with glioma (hematuria within 24 h) [23]	The combination described should not be used [23]
Azole antifungals (fluconazole, voriconazole, posaconazole)	Inhibitors of CYP3A4 and P-glycoprotein. Fluconazole and voriconazole also inhibit CYP2C9 and 2C19 [23]	Vinca alkaloids [23]	Azole antifungals used with vinca alkaloids can cause neurotoxicity [23]	Stop the use of these antifungals 24 h before chemotherapy and resume 24 h later; if this is not possible, an antifungal from the class of echinocandins (e.g., micafungin or caspofungin) should be used [23]

(continued)

Table 4.14 (continued)

Drug	Enzyme complex, protein, or cause of interaction	Drug that interacts	Interaction	Clinical action
Azole antifungals (fluconazole, voriconazole, posaconazole)	Inhibitors of CYP3A4 and P-glycoprotein. Fluconazole and voriconazole also inhibit CYP2C9 and 2C19 [23].	Cyclosporine and tacrolimus [23].	Increase in serum levels of cyclosporine and tacrolimus [23].	The dose of cyclosporine should be reduced by 50 % and that of tacrolimus should be reduced by 66 % of the normal dose [15].
Itraconazole	Inhibitor of CYP 3A4 and P-glycoprotein [15].	Drugs that inhibit CYP3A4 or P-glycoprotein [15].	Itraconazole with inhibitors of CYP3A4 or P-glycoprotein causes exacerbated hepatotoxicity [15].	Concomitant use is contraindicated [15].

4.12 Mercaptopurine and Allopurinol

Mercaptopurine is a prodrug that can undergo intracellular catabolism to the inactive metabolite 6-methylmercaptopurine or anabolism to the active metabolite 6-methylmercaptopurine nucleotide (6-MMPN); both forms are converted by the enzyme thiopurine methyltransferase (TPMT), and there is variability between TPMT activity among patients. The dose of mercaptopurine, when combined with allopurinol, should be significantly reduced, because allopurinol inhibits the first-pass metabolism of mercaptopurine and decreases the conversion of 6-mercaptopurine to the inactive form 6-thiouric acid, thereby increasing the available form of the drug for anabolism to the active form (6-MMPN) [62, 105].

Chapter 5
Drug – Food Interactions

List of tables

5.1 Interactions Involving Food and Chemotherapy

St. John's wort, similarly to steroid hormones and some phytotherapeutic drugs, may increase hepatic levels of CYP3A4, accelerating the metabolism of some drugs. Also, several foods contain inhibitors or inducers of CYP, thus influencing the metabolism and toxicity of drugs. Grapefruit juice is a strong inhibitor of CYP3A4, and may increase the bioavailability of drugs metabolized by CYP3A4. Individual differences in CYP polymorphisms have an influence on drug metabolism [5, 6, 105].

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All nutritional supplements should be reviewed when the patient is undergoing cancer treatment, because many foods and supplements may alter the therapeutic efficacy and toxicity of chemotherapeutic drugs.

St. John's wort induces CYP3A4, 2D6, 2C9, and 1A2, and so may increase the clearance of chemotherapy drugs metabolized by these cytochrome enzymes, reducing these drugs' effects [23, 105].

Multivitamins containing folic acid may reduce the therapeutic efficacy of methotrexate, taking into account the mechanism of action of methotrexate – a structural analogue of folic acid – which is a folic acid inhibitor [23].

Mercaptopurine oral may be best absorbed if taken 1 h before or 2 h after the last meal, although dairy or calcium products should be avoided within 2 h of the dose [67, 104]. Mercaptopurine is inactivated by xantine oxidase; therefore, this substance may potentially reduce the bioavailability of mercaptopurine. Cow's milk contains a high level of xanthine oxidase and should be avoided with mercaptopurine. This interaction may be clinically significant [68].

For temozolomide oral, the absorption of the medication can be reduced if it is taken with food, thus the increasing its adverse effects [67].

Melphalan oral has a reduced effect if taken with food [67].

Table 5.1 Drug interactions involving St. John's Wort and chemotherapy

Drug	Enzymatic complex that metabolizes and can be induced by St. John's wort	Result of the interaction
Cyclophosphamide	CYP3A4	Increase of clearance, decreased effect.
Docetaxel	CYP3A4	Increase of clearance, decreased effect.
Doxorubicin	CYP2D6 and CY3A4	Increase of clearance, decreased effect.
Etoposide	CYP3A4	Increase of clearance, decreased effect.
Ifosfamide	CYP3A4	Increase of clearance, decreased effect.
Irinotecan	CYP3A4	Increase of clearance, decreased effect.
Lomustine	CYP2D6	Increase of clearance, decreased effect.
Paclitaxel	CYP2C9 and CYP 3A4	Increase of clearance, decreased effect.
Vinblastine	CYP3A4	Increase of clearance, decreased effect.
Vincristine	CYP3A4	Increase of clearance, decreased effect.
Vinorelbine	CYP3A4	Increase of clearance, decreased effect.

Source: Based on information from Bragalone [4]

Table 5.2 Drug interactions involving grapefruit and chemotherapy

Drug	Enzymatic complex that metabolizes and can be inhibited by grapefruit	Result of the interaction
Cyclophosphamide	CYP3A4	Decrease of clearance, increased effect [5, 6].
Docetaxel	CYP3A4	Decrease of clearance, increased effect [5, 6].
Doxorubicin	CYP2D6 and CYP3A4	Decrease of clearance, increased effect [5, 6].
Etoposide	CYP3A4	Decrease of clearance, increased effect [5, 6].
Ifosfamide	CYP3A4	Decrease of clearance, increased effect [5, 6].
Irinotecan	CYP3A4	Decrease of clearance, increased effect [5, 6].
Lomustine	CYP2D6	Decrease of clearance, increased effect [5, 6].
Paclitaxel	CYP2C9 and CYP3A4	Decrease of clearance, increased effect [5, 6].
Vinblastine	CYP3A4	Decrease of clearance, increased effect [5, 6].
Vincristine	CYP3A4	Decrease of clearance, increased effect [5, 6].
Vinorelbine	CYP3A4	Decrease of clearance, increased effect [5, 6].

Table 5.3 Drug interactions involving food and chemotherapy

Drug	Food that interacts	Result of the interaction
Melphalan oral	Food	Melphalan oral has a reduced effect if taken with food [67]
Mercaptopurine	Dairy products with calcium, such as cow's milk; or calcium products	Mercaptopurine is inactivated by xanthine oxidase; therefore, products that contein this substance may potentially reduce the bioavailability of mercaptopurine. This interaction may be clinically significant Avoid dairy or calcium products within 2 h of taking the dose [67].
Methotrexate	Folic acid, or multivitamins that contain folic acid	Reduction of therapeutic efficacy due to the mechanism of action of methotrexate, a structural analogue of folic acid that is a folic acid inhibitor [23].
Temozolomide oral	Food	For temozolomide oral, absorption of the medication can be reduced if it is taken with food, thus increasing its adverse effects [67].

Appendix

This appendix provides an overview of essential things to know in pediatric oncology practice, such as how to calculate body surface area in children, and how to calculate the carboplatin dose using the area under the curve and the estimated creatinine clearance.

A glossary of terms used in the book is also provided.

List of tables

Body Surface Area (BSA) [4]

The body surface area (BSA) is a mathematical relationship, expressed in m^2, with the result obtained from the height and weight of the patient. This measure is used in order to obtain a more comprehensive parameter of the patient's weight, to define more appropriate dosage. The BSA is widely used in oncology; the majority of protocols specify the dose in m^2.

$$\text{BSA } (m^2) = \frac{\left(\text{Weight}\left(\text{kg}\right)^{0.425} \times \text{Height}\left(\text{cm}\right)^{0.725} \times 71.84\right)}{10,000}$$

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$$\log \text{BSA } (m^2) = \frac{(\log kg \times 0.425) + (\log cm \times 0.725) + 1.8564}{10,000}$$

$$\text{DuBois Formula: BSA } (m^2) = \sqrt{\frac{\text{Height}(cm) \times \text{Weight}(kg)}{3,600}}$$

Calculation of Carboplatin Dose

Carboplatin is excreted almost entirely by glomerular filtration; therefore, it has a half-life that is highly correlated with the classification of glomerular filtration, and the area under the curve (AUC) is essential for the determination of the individual patient dose. Therapy may be optimized by being based on a wide variety of methods of analysis of renal clearance. Studies of doses and chemotherapy protocols often use the AUC for calculate carboplatin doses, and these doses are not described in m^2 [1].

Carboplatin dose in mg = Desired AUC × (25 + measured or estimated creatinine clearance) [4].

Estimated Creatinine Clearance [4]

This measure is used for patients with normal renal function, except when the serum creatinine changes quickly or when the patient has marked edema. Indicated only for children over 6 months old.

Table 1 Constant of Proportionality for Estimated Creatinine Clearance

Age	***K***
<1 year (preterm)	0.33
< 1 year (full-term)	0.45
1–12 years old	0.55
13–21 years old, female	0.55
13–21 years old, male	0.70

Source: Based on information from Bragalone [4, 66]

Creatinine clearance (mL/min/1.73 m^2) = K × Height (cm)/Scr (mg/dL)

Scr: Serum creatinine in mg/dL

K: Constant of proportionality, as shown in Table 1

The following formula can be applied for children and adolescents between 1 and 18 years old: Crcl (mL/min/1.73 m^2) = 0.48 × Height (cm)/Scr (mg/dL)

Glossary

Aminoglycosides Class of bactericidal antibiotics that act by inhibition of bacterial protein synthesis; examples are amikacin, gentamicin, neomycin, and tobramycin.

Anthracyclines Class of antineoplastic drugs with various mechanisms of action; this class includes doxorubicin, daunorubicin, and idarucibin.

Antibiotics derived from penicillin Class of antibiotics that includes many drugs derived from penicillin; most commonly used are amoxicillin and ampicillin.

ATRA (trans-retinoic acid) syndrome Characterized by fever, pulmonary infiltrates, pleural or pericardial effusion, and renal failure. It may occur usually 2–10 days after treatment and is reversible with the temporary suspension of ATRA and treatment with dexamethasone 0.5–2 mg/kg.

Auer rods Auer rods are lysosomal compounds that can be seen in the blasts of some acute leukemias of myeloid lineage; they contain peroxidase, lysosomal enzymes, and large crystalline inclusions.

Azole antifungals Class of antifungals (fungistatics), with a broad spectrum of action; examples are fluconazole and voriconazole.

Bcr-abl protein (hybrid) This protein is the result of translocation between the long arms of chromosomes 9q34 and 22q1 (Philadelphia chromosome); this protein has increased tyrosine kinase activity.

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Chloroma Chloroma is the same as granulocytic sarcoma and extramedullary myeloid tumor, which is a tumor of myeloblasts or immature myeloid cells that appears in extramedullary locations.
Cytochrome P450 Family of metabolizing enzymes.
Down syndrome Most cases are caused by trisomy of chromosome 21, but cases can occur by the translocation of chromosome 21 and other chromosomes.
Dynamic equilibrium Dynamic equilibrium occurs when there is linearity and constancy in the bioavailability of a drug.
Echinocandins Class of antifungal drugs that inhibit the synthesis of β-d-glucan in fungal cell walls. Exemples of echinocandins are micafungin and caspofungin.
Free drug Drug that is not bound to a protein or enzyme.
Hydrophobic substances These are non-polar; they tend to not mix with water.
Hydrolytic substances These are polar; they tend to mix with water.
Isoenzymes Enzymes that differ in amino acid sequence and catalyze the same chemical reactions.
Lymphocyte predominant cells Called popcorn cells, lympho-histiocytic cells, or LP cells. These are a variant of Reed Steinberg cells, which exhibit a lobed and bent nucleus, with inconspicuous nucleolus.
Macrolides Class of antibiotics that inhibit bacterial protein synthesis. Their action can be bacteriostatic or bactericidal (at high concentrations or depending on the microorganism).
Narrow therapeutic dose This is the area between the minimum effective dose and the maximum dose.
Pancytopenia Reduction of leukocytes, erythrocytes, and platelets; all reduced at the same time.
pH Potential of hydrogen, used to measure acidity or alkalinity.
Philadelphia chromosome This chromosome is the result of translocation between the long arms of chromosomes 9q34 and 22q1.
pKa Acid dissociation constant.

Platinum compounds Class of drugs, with many mechanisms of action, such as carboplatin and cisplatin.
Reed Sternberg Cells Clonal B-lymphocytes that do not produce immunoglobulin nor possess functional B-receptors; they are giant cells, bi- or multinucleated.
Stem cell This is an undifferentiated cell that can undergo differentiation to a specific type of cell.
Vinca alkaloids Class of alkaloid drugs, such as vincristine, vinblastine, and vinorelbine, extracted from a plant called vinca.
Xenobiotics Compounds synthesized industrially and not found in nature.

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