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Treatment of Pediatric Acute Lymphoblastic Leukemia and Recent Advances

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1. Introduction

Pediatric acute lymphoblastic leukemia (ALL) is the most prevalent cancer in children. Today in developed countries around 80% of children with ALL can achieve 10 year survival. This great improvement in treatment outcomes for pediatric ALL is due to several important advances which have taken place since the 1960s, including intensive induction/consolidation chemotherapy regimens, risk-adapted therapy, central nervous system prophylaxis, aggressive supportive care (especially prophylaxis and treatment for infections) and minimal residual disease detection. Rapid progress in molecular biology has helped to select patients with specific poor prognostic genetic factors and sensitive monitoring of minimal residual disease has also contributed significantly to the management of pediatric ALL. However, patients with extremely poor prognostic factors or delayed response to chemotherapy still experience disease relapse. Hematopoietic stem cell transplantation (HSCT), mainly using allogenic stem cells (bone marrow, peripheral blood or umbilical cord blood stem cells), has been proven to be an effective alternative and to ensure long-term survival for patients with relapsed ALL or with extremely poor prognostic factors. However, there are complications such as severe infections and chronic graft-versus-host disease (GVHD) that may be occurred. Recent advances in the development of new formulations of existing drugs, targeted therapy and immunotherapy provide new options in treatment of patients with refractory disease and promise to further improve of the cure rates of pediatric ALL.

2. Characteristics of pediatric acute lymphoblastic leukemia

Leukemia is the most common malignancy in the pediatric population, comprising 30% of malignant tumors in children (Chiang et al., 2010; Young and Miller, 1975). The most prevalent subtypes of pediatric leukemia are acute lymphoblastic leukemia (75~80%) and acute myelogenous leukemia (15~17%)(Feltbower et al., 2009).
Common presenting symptoms of pediatric ALL include fever, pallor, hepatosplenomegaly, lymph node swelling and hemorrhage. Bone pain or arthralgia is sometimes reported. The diagnosis of pediatric ALL is based on examination of cell morphology, cytochemistry and immunochemical analysis of bone marrow aspirates. Pediatric ALL can be classified according to different characteristics: L1, L2 or L3 by morphology, and B-cell, T-cell, co-expression of myeloid antigens or mixed type by immunophenotyping. Risk-adapted

therapy is the main strategy for pediatric ALL treatment and has achieved a 5-year event-free survival rate of approximately 80% in recent years.

3. Chemotherapy

3.1 Basic treatment principles

Treatment for pediatric ALL comprises two major components: multi-drug combination chemotherapy and intrathecal (IT) chemotherapy for central nervous system (CNS) prophylaxis. Modern protocols have a number of design elements in common including a remission induction phase, a consolidation/intensification phase, and a CNS treatment and continuation (maintenance) phase, with or without delayed intensification (Provan et al., 2009). Multi-drug combination chemotherapy has been the mainstay of ALL management since the late 1960s and a major survival improvement was achieved when 8-week, 8-drug induction/consolidation regimens followed by maintenance therapy were introduced in the 1970s. CNS prophylaxis therapy with IT chemotherapy alone or with cranial radiation was added to the treatment regimen after the induction phase and markedly reduced CNS involvement in leukemia from around 80% to 4~6%(Evans et al., 1970; Moghrabi et al., 2007; Pui, C.H. et al., 2009). Following consolidation treatment, maintenance chemotherapy is initiated and continued for 2~3 years.

3.2 Evolution of regimens

During the late 1960s and early 1970s, patients with pediatric ALL were treated with a three-drug regimen (vincristine, prednisolone and asparaginase) to induce remission, CNS prophylaxis therapy with weekly IT methotrexate (MTX) and cranial radiation was performed during the intensification phase followed by continuation treatment consisting of daily oral mercaptopurine, weekly oral MTX and monthly pulses of prednisolone and vincristine (Schrappe et al., 2010). Later, an early multiple agent induction/consolidation regimen was developed by Dr Riehm (Riehm et al., 1977). This comprised 8-drug induction chemotherapy for 9 weeks (prednisolone, daunorubicin, vincristine, asparaginase, methotrexate, mercaptopurine, cyclophosphamide and cytarabine) and 4 cycles of high-dose methotrexate (HDMTX) with daily oral mercaptopurine for 8 weeks. This improved the cure rate to over 50%. The high remission rate was thought to be related to the intensified remission induction phase. The requirement for precise and robust supportive care in specialized hospitals undertaken by experienced medical staff was emphasized in order to control treatment-related complications (Riehm et al., 1977; Schrappe et al., 2010). This approach remains at the core of modern pediatric ALL regimens.

Risk-adapted therapy stratified by age and initial white blood cell count was demonstrated to increase the remission rate in poor risk groups and to decrease acute and chronic toxicities in good risk groups (Henze et al., 1981). The system of risk classification based on age and white blood cell count was extended by addition of other important prognostic factors for pediatric ALL (Table 1). The application of risk-adapted therapy in clinical trials has resulted in a steady improvement in the outcome of pediatric ALL, with a current overall survival rate of around 80% in developed countries (Jeha and Pui, 2009). The significance of early response to induction treatment , as measured by reduction in peripheral blood blast cells, was proposed in 1987 and used as an indicator to divide patients into different risk groups (Riehm et al., 1987). Since then, many more prognostic

factors have been identified and integrated into risk-classification systems. With the advances in genome-wide screening techniques, pharmacogenomic studies, and development of molecular therapeutics an era of more refined personalized therapy is anticipated (Pui, C.H., 2010).

Risk group	Age (y)	Leukocyte count (/ul)	Immunophenotype	Chromosome	Genotype	Early response to chemotherapy#
Low	1-9	<50, 000	Precursor B-cell	Hyperdiploidy*	*TEL-AML1*	Good
High	<1 or ≧10	>50, 000	T-cell	Hypodiploidy*	*MLL-AF4 BCR-ABL*	Poor

*hyperdiploidy: >50 chromosome; hypodiploidy: <44 chromosome
#defined as MRD at the end of induction chemotherapy (good response: MRD<0.01%; poor response: MRD≧1%)

Table 1. Prognostic factors used for risk classification in pediatric ALL (adapted from (Pui, C.H., 2010) with permission)

National and international treatment groups have been established worldwide with the objective of improving the management of childhood ALL. The long-term results of recently completed clinical trials are listed in Table 2 (Conter et al., 2010; Gaynon et al., 2010; Liang et al., 2010; Mitchell et al., 2010; Moricke et al., 2010; Pui, C.H. et al., 2010). In Taiwan, the Taiwan Pediatric Oncology Group was formed in 1988 and marked progress in ALL treatment has been achieved with overall survival increasing from 59% during 1988~1995 to 82% during 2003~2009.

Study group	Trial	Year	Case number	10-year EFS (%)	10-year OS (%)
CCG	CCG-1900	1996-2002	4464	72.6	82.1
AIEOP	AIEOP-ALL 95	1995-2000	1743	71.7	82.4
BFM	ALL-BFM 95	1995-2000	2169	78	85
SJCRH	Total 13B	1994-1998	247	80.1*	85.7*
SJCRH	Total 14	1998-1999	53	79.2	77.4
SJCRH	Total 15	2000-2007	498	85.6*	93.5*
UK-WPCL	UKALL 97	1997-2002	1948	74	83
TPOG	TPOG-2002	2002-2007	788	77.4*	83.5*

CCG: Children's Cancer Group; AIEOP: Associazione Italiana di ematologia ed Oncologia Pediatrica; BFM: Berlin-Frankfurt-Munster ALL Study Group; SJCRH: St Jude Children's Research Hospital; UK-WPCL: UK Medical Research Council Working Party on Childhood Leukemia; TPOG: Taiwan Pediatric Oncology group; EFS: event-free survival; OS: overall survival ; *5-year EFS and OS

Table 2. Treatment outcomes for selected pediatric ALL study groups

3.3 Central nervous system treatment
Early in the 1960s central nervous system(CNS) treatment was applied to the "total" therapy for pediatric ALL since it was found that better control of systemic leukemia was

accompanied by increased frequency of CNS involvement (Aur, R.J. and Pinkel, 1973; Simone, J.V., 1973). Radiation therapy of the CNS and IT MTX administration were the two main strategies for preventing CNS disease (Glidewell and Holland, 1973; Kim et al., 1972; Rosner and Grunwald, 1973; Simone, J. and Pinkel, 1973). Dosage and treatment modalities of CNS radiation were studied in an attempt to reduce neurotoxicities while maintaining effectiveness (Simpson et al., 1973). The St. Jude leukemia group compared cranial radiation with IT MTX and craniospinal irradiation in clinical trials and suggested that combined cranial radiation and IT MTX treatment was as effective as craniospinal irradiation with fewer toxicities (leukopenia and interruption of treatment)(Aur, R.J.A. et al., 1973). Since then, combined cranial irradiation and IT MTX have become the standard treatment for preventing CNS disease. However, further studies revealed that survivors of pediatric ALL who received high doses of cranial irradiation (over 25 Gy) or who were treated at a young age (younger than 2 years) suffered from significant long-term sequelae, such as defective cognitive function and secondary malignancy (Moe and Holen, 2000; Spiegler et al., 2006). Therefore, some study groups suggested that the dose of radiation be decreased to less than 18 Gy (Henze et al., 1983) or that the extended IT MTX treatment be used as a replacement for cranial irradiation in low-risk patients (Conter et al., 1995). However, some treatment groups preferred to continue to employ cranial irradiation because of the poor prognosis with CNS leukemia (Gelber et al., 1993). After a lengthy debate regarding the role of cranial irradiation in pediatric ALL treatment, Pui CH et al. published their study results in this issue and suggested that 'with effective risk-adjusted chemotherapy, prophylactic cranial irradiation can be safely omitted from the treatment of childhood ALL'(Pui, C.H. et al., 2009).

4. Minimal residual disease

Complete remission of ALL has been defined as blastic cells less than 5% of nucleated cells on bone marrow smear. Before the introduction of molecular methods or multicolor flow cytometry techniques, the percentage of blastic cells was measured by morphology, with a sensitivity of 1%. During the last twenty years, rapid progress in molecular biology has greatly improved the sensitivity of residual blastic cell detection, especially in the range 1% to 0.01%, which is designated minimal residual disease (MRD) (Campana and Pui, 1995; Neale et al., 1994). A new definition of remission was then established on the basis of immunologic or molecular response. A better clinical outcome is predicted in patients who achieve 'immunologic' or 'molecular' remission (ie leukemic involvement of <0.01% of nucleated bone marrow cells after initial intensive chemotherapy) compared with patients whose remission is defined solely by morphologic criteria (Coustan-Smith et al., 2000; Pui, C.H. and Campana, 2000). Among the various methods using immunologic or molecular characteristics of blastic cells as markers, the most promising are flow cytometric detection of aberrant immunophenotypes, and polymerase chain reaction analysis of clonal antigen-receptor gene rearrangements or leukemia-specific fusion genes (Campana and Pui, 1995; Coustan-Smith et al., 1998; Ludwig et al., 1990; van Dongen et al., 1999). Taken together, almost all patients with pediatric ALL can be monitored for MRD during the course of treatment (Campana et al., 2001; Chen et al., 2001; Neale et al., 2004; Pui, C.H. and Campana, 2000). Recent studies indicated that monitoring of MRD constituted an essential prognostic marker, and that detection of MRD, particularly at the end of induction and after treatment

completion, was significantly predictive for patient outcome (Katsibardi et al., 2010; Stow et al., 2010).

5. The role of hemopoietic stem cell transplantation in pediatric acute lymphoblastic leukemia

Hemopoietic stem cell transplantation was introduced for children with ALL in the 1970s. Along with the significant improvements in clinical outcome observed in patients receiving chemotherapy, HSCT became the treatment choice for relapsed cases and patients with poor prognostic factors (Gratwohl et al., 1990; Makipernaa et al., 1995; Uderzo et al., 1995). In early studies, 40 to 50% of relapsed patients achieved long remissions and were potentially cured by marrow transplantation. However, the effectiveness of the approach was diminished by the problems of acute and chronic GVHD, infection, and relapse(Johnson, 1990; Moussalem et al., 1995; Pinkel, 1994; Wingard et al., 1990). Currently, HSCT is only considered in patients with extremely poor prognostic factors (for example, Philadelphia chromosome positive [PH+] ALL with poor response to induction therapy), with delayed response to chemotherapy (induction failure, MRD >1% on the end of remission date or MRD >0.01% prior to reinduction of chemotherapy) and in patients who experience early relapse (Arico et al., 2010; Burke et al., 2009; Davies and Mehta, 2010; Pulsipher et al., 2011).

6. Recent advances in therapy and research in pediatric ALL

Philadelphia chromosome-positive ALL has been found to be associated with a poor response to conventional chemotherapy and a high relapse rate, especially in patients older than 10 years (Arico et al., 2010). HSCT has been employed in patients with PH+ ALL in an attempt to improve long-term outcomes. In the early 2000s, BCR-ABL targeted strategies started to be incorporated into the treatment for PH+ ALL. Imatinib, a first generation tyrosine kinase inhibitor, showed its efficacy in improving the treatment outcome in PH+ALL with or without HSCT (Alvarado et al., 2007; Carpenter et al., 2007; Champagne et al., 2004; Fuster et al., 2007; Jones, L.K. and Saha, 2005). Given the marked improvement in treatment results achieved with combinations of a tyrosine kinase inhibitor (imatinib) and intensive chemotherapy, transplantation is not recommended for the first remission of children with PH+ ALL, unless the early response to treatment was poor (Barr, 2010; Gruber et al., 2009; Koo, 2011; Liu et al., 2009; Milone and Enrico, 2009; Ottmann and Pfeifer, 2009; Schultz et al., 2009). Second generation tyrosine kinase inhibitors were developed because imatinib may induce specific resistance mainly due to ABL1 mutations. Dasatinib, a multi tyrosine kinase inhibitor targeted to BCR-ABL, SRC, C-KIT, PDGFR and ephrin A receptor kinase, and nilotinib, another BCR-ABL targeted agent similar to imatinib but with a higher affinity, are two novel agents with the potential to address PH+ALL resistance to imatinib (Alvarado et al., 2007; Aplenc et al., 2011; Kawaguchi et al., 2005; Kolb et al., 2008; Linger et al., 2009; Piccaluga et al., 2007; Porkka et al., 2008).

Mixed lineage leukemia (MLL) rearrangements occur in 80% of infants and 5% of older children with ALL. MLL-rearranged ALL patients have poor treatment outcomes with conventional chemotherapy. FLT3 (FMS-like tyrosine kinase receptor-3) is one of the unique gene expression profiles in MLL-rearranged ALL. Eighteen percent of MLL-rearranged ALL harbored activating mutations of FLT3 with high expression levels (Armstrong et al., 2003; Brown et al., 2005). *In vitro* studies have demonstrated that FLT3 inhibitor, CEP-701,

effectively suppresses FLT3 driven leukemic cell survival (Brown et al., 2006; Brown et al., 2005).

Monoclonal antibodies, including rituximab (anti-CD20), epratuzumab (anti-CD22), inotuzumab (anti-CD22), recombinant immunotoxins and bispecific antibodies (blinatumomab) and radioimmunotherapy have already been incorporated into clinical trials or are undergoing investigation. (Attias and Weitzman, 2008; Christiansen and Rajasekaran, 2004; Dworzak et al., 2008; Oriuchi et al., 2005; Reichert and Valge- Archer, 2007; Topp et al., 2011)

The application of emerging DNA and RNA techniques, SNP arrays, DNA methylation arrays and genome-wide association studies has led to the discovery of further genetic and epigenetic alterations. IKZF1, JAK mutations, and CDKN2A/B are among several examples which have been shown to be related to leukemogenesis and drug resistance (Davidsson et al., 2009; Yang et al., 2009; Yu et al., 2011). MicroRNAs alterations and dysregulation of DNA methylation have also been found in children with ALL and are being assessed as new targets for treatment (Bachmann et al., 2010; Davidsson et al., 2009; Herman et al., 1996; Schotte et al., 2011). In the near future, more individualized treatment strategies will be established based on detailed genetic and epigenetic characteristics, response to early treatment and MRD monitoring Such strategies will require precise supportive care.

7. Supportive care

7.1 Tumor lysis syndrome

Tumor lysis syndrome (TLS) is a well-recognized complication of leukemia and lymphoma, especially in patients with B-cell or T-cell neoplasms and a large tumor burden (Alperin and Levin, 1964; Cohen et al., 1980; Jones, D.P. et al., 1990; Kedar et al., 1995; Kuhbock et al., 1968; Rieselbach et al., 1964). TLS may occur spontaneously or during the early phase of treatment and can lead to severe metabolic disturbances (hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia) (Jones, D.P. et al., 1995). TLS-associated hyperuricemia may cause acute renal failure because of the rapid and dramatic increase of uricemia and renal burden of uric acid urate. Without appropriate management, precipitation of uric acid crystals can obstruct the tubules and collecting ducts, resulting in tubular necrosis and renal failure (Renyi et al., 2007). Allopurinol, which is an inhibitor of the enzyme xanthine oxidase, combined with hydration, osmotic diuretics and urinary alkalization has been the standard treatment for TLS since the late 1960s and remains an important part of leukemia treatment (Aviles, 1995; DeConti and Calabresi, 1966; Holland and Holland, 1968; Jones, D.P. et al., 1995; Rundles, 1966; Watts, 1966). Through blocking uric acid formation, allopurinol can effectively lower the serum uric acid level, but it increases the renal load of hypoxanthine and xanthine (both are uric acid precursors) (Andreoli et al., 1986; DeConti and Calabresi, 1966). Allopurinol treatment has been associated with xanthine nephropathy and calculi because xanthine is actually less soluble than uric acid in urine (Band et al., 1970; Wyngaarden, 1970). Moreover, allopurinol may interact with chemotherapy agents and affect drug metabolite concentrations (Rundles, 1966).

Urate oxidase, an endogenous enzyme in most mammals but not in humans, can act as a catalyst in the oxidation of uric acid to allantoin. Because allantoin is five to ten-fold more soluble than uric acid, urate oxidase can effectively decrease uric acid levels in patients with TLS (Brogard et al., 1972). Recombinant urate oxidase was introduced in France in 1975. During the 1980s and 1990s, non-recombinant urate oxidase (Uricozyme; Sanofi-Synthelabo,

Inc, Paris), purified from cultures of Aspergillus flavus, was used in the treatment of TLS in ALL patients (Masera et al., 1982). Although it improved the elimination of uric acid, however, this agent was found to be associated with allergic reactions (rashes, bronchospasm , urticaria and angioedema) in about 5% of patients, even in those without a history of allergy (Patte et al., 2001; Pui, C.H. et al., 1997). A new urate oxidase (rasburicase) was developed by use of a recombinant DNA technique in 1996 (Cammalleri and Malaguarnera, 2007). This approach allowed more rapid production of greater quantities of urate oxidase. Rasburicase is purer than non-recombinant urate oxidase, has greater activity and lower allergic reaction rates. Studies of the use of rasburicase in patients with ALL, have shown it to be a safe and effective alternative to allopurinol for the prevention and treatment of hyperuricemia (Cammalleri and Malaguarnera, 2007; Cheson and Dutcher, 2005; Lee et al., 2003; McNutt et al., 2006; Patte et al., 2001; Pui, C.H., 2001; Sood et al., 2006; Wang et al., 2006). The toxicity of rasburicase is negligible, although the presence of anti-rasburicase antibodies has been reported in some patients (Pui, C.-H. et al., 2001).

7.2 Infections

Neutropenia is usually found when ALL is newly diagnosed or during chemotherapy, especially induction therapy. Children with ALL and disease-induced or treatment-related neutropenia, (usually defined as absolute neutrophil count less than 500 per mm^3) are more prone to severe bacterial, fungal and viral infections (Freifeld et al., 2011). More febrile neutropenia episodes occur during induction of remission than during remission in children with ALL. The risk of severe infection is high with severe neutropenia (less than 200 per mm^3)(Jones, G.R. et al., 1996; Peng et al., 1981). Both the degree and duration of neutropenia affect the risk of infection. For the purpose of managing febrile neutropenia, patients have been categorized into different risk groups. Rackoff et al. classified patients with febrile neutropenia into three risk groups based on the absolute monocyte count and temperature at the time of admission. They found that the odds ratio of bacteremia for the high-risk versus the intermediate-risk group is 4.4 (no bacteremia episodes were found in the low-risk group)(Rackoff et al., 1996). The Infectious Disease Society of America (IDSA) started categorizing patients with febrile neutropenia in 2002 and the updated recommendation published in 2010 divided these patients into high-risk or low-risk groups according to the presenting symptoms and signs, neutrophil counts, underlying cancer, type of therapy, the anticipated length of neutropenia and medical comorbidities. The high-risk group was defined when any of the following criteria applied : profound neutropenia anticipated for longer than 7 days, evidence of hepatic or renal insufficiency, comorbidities with unstable vital signs, severe mucositis, gastrointestinal symptoms, neurological symptoms, catheter-related infections, new pulmonary infiltration or hypoxia (Freifeld et al., 2011). It was suggested that high-risk patients be admitted at once and that antibiotics should be administered on an empirical basis as soon as possible. Worldwide, the etiology of infections is now predominantly due to Gram-positive bacterial pathogens. In a study conducted in 1981, Gram-positive and Gram-negative bacteria were equally represented (Peng et al., 1981). In another study, Gram-negative bacteria accounted for the great majority of the etiologic agents (Escherichia coli, Klebsiella spp. and Pseudomonas aeruginosa were the three most common pathogens) (Bodey et al., 1978). Recent studies have showed that Gram-positive bacteria account for more than fifty percent of bacterial episodes with coagulase-negative staphylococci, viridans streptococci and Staphylococcus aureus being the most common pathogens (Hakim et al., 2009).

Systemic (invasive) fungal infections are another common infection in patients with febrile neutropenia. ALL was the second most common underlying disease associated with proven invasive fungal infections after acute myelogenous leukemia in children treated for cancers (Mor et al., 2011). In earlier studies, systemic fungal infections occurred in around 20% of cases of pediatric acute leukemia during induction chemotherapy and the duration of neutropenia was a significant risk factor (Wiley et al., 1990). In the late 1990s, when antifungal prophylaxis and early initiation of empirical antifungal therapy were introduced, the rate of invasive fungal infections decreased, although the rate of fungal colonization in children receiving remission induction therapy for acute leukemia was still high (Gozdasoglu et al., 1999). In a study conducted in 2007, the occurrence of invasive fungal infections was monitored after renovation of the ventilation system on a pediatric hematology/oncology unit and initiation of routine azole antifungal prophylaxis. The incidence of proven invasive fungal infection was 3.2% (1/31) in the allogenic stem cell transplant group, 0/26 in autologous stem cell transplant group and 1.6%(1/60) in the induction therapy group (Hovi et al., 2007). In 2010, IDSA guidelines proposed antifungal prophylaxis administration in high-risk groups, and empiric antifungal therapy or preemptive therapy in patients with febrile neutropenia 4-7 days after broad-spectrum antibiotics treatment (Freifeld et al., 2011). However, a shift of fungal pathogens from Candida sp. towards mold infections was observed along with the increasing use of antifungal prophylaxis. In a recent study which enrolled 1047 children with different malignancies, 20% of the proven invasive fungal infections had candidemia and 80% had mold infections. Non-albicans candida accounted for 60% of all candidemia and 55% of mold infections were non-Aspergillus (Mor et al., 2011). Although the incidence of and mortality due to invasive fungal infections were both lower than previously reported, the epidemiologic spectrum of fungus isolates has broadened and this should be considered in the selection of antifungal agents for prophylaxis or empirical treatment.

Granulocyte-colony stimulation factor (G-CSF) or granulocyte-monocyte colony stimulating factor (GM-CSF) have the potential benefits of reducing the duration of neutropenia and, in turn, the risk of infection. A meta-analysis of 16 randomized controlled trials concluded that prophylactic use of G-CSF or GM-CSF was associated with a 20% reduction in febrile neutropenia and a two-day decrease in duration of hospitalizations (Sung et al., 2004). IDSA 2010 guidelines recommend prophylactic use of G-CSF or GM-CSF for patients in whom the predicted risk of fever and neutropenia is over 20% (Freifeld et al., 2011).

8. Conclusion

Pediatric ALL is the most common malignancy in children. The cure rates of pediatric ALL have improved greatly through use of risk-adapted therapy and aggressive supportive care. Advances in molecular biology and high-throughput technology will allow further investigation of the mechanisms of leukemogenesis and disease relapse and will, in turn, lead to more sophisticated treatments in the future.

9. Acknowledgements

10. References

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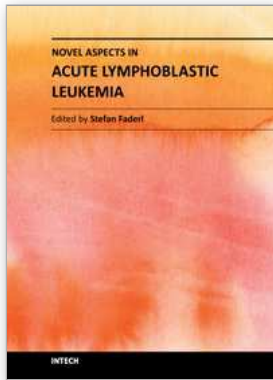
Acute lymphoblastic leukemia (ALL) has turned from a universally fatal to a highly curable disease in little more than four decades. Even though differences in outcome continue to exist between children and adults, intense efforts are under way to overcome this discrepancy and improve the prognosis of adult patients as well. This exemplary progress in ALL therapy has been possible by the combination of an increasingly better understanding of the biology of the disease, availability of a range of effective drugs, and astute designs and relentless executions of many clinical trials. ALL is a complex disease requiring complex therapy. Whereas this book cannot provide a comprehensive review of every one of its many facets, the chapters from many investigators from around the world nevertheless cover a number of relevant topics: aspects of the epidemiology of ALL in Hispanics, ophthalmologic manifestations of ALL, overviews of current therapy and drug-resistance mechanisms, novel biological pathways and targets, new drugs in development, and long-term consequences of CNS prophylaxis and therapy. The publishers and editor therefore hope that the prospective readers will find enough insight and information for their own endeavors.

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