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Global efforts toward the cure of childhood acute lymphoblastic leukemia

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Abstract

Recent improvements in risk-directed treatment and supportive care, together with greater reliance on both national and international collaborative studies, have made childhood acute lymphoblastic leukemia (ALL) one of the most curable human cancers. Next-generation sequencing studies of leukemia cells and the normal host genome provides exciting opportunities for precision medicine and thus the cure rate and quality of life of the patients. Efforts are under way to assess the global impact of childhood ALL and to develop initiatives that can meet the long-term challenge of providing quality care to the world's children with this disease and improving cure rates globally. This ambitious task will rely greatly on increased collaborative research and international networking, so that the therapeutic gains in high-income countries can be translated to patients residing in low- and middle-income countries. Ultimately, the greatest obstacle to overcome will be to fully understand leukemogenesis, enabling measures to decrease the risk of leukemia development and thus close the last major gap in our ability to offer a cure to any child who may succumb to this disease.

Introduction

Advances in the biologic study and treatment of childhood acute lymphoblastic leukemia (ALL) are one of the most successful stories of modern medicine[1]. Over the past five decades, this once uniformly fatal disease has been transformed to one with a 5-year survival rate exceeding 90% among children receiving protocol-directed treatment in most developed countries (Table 1)[2–14]. This improved outcome can be attributed to advances in supportive care, more accurate diagnosis, and optimal risk-directed therapy incorporating consolidation

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treatment with high-dose or escalating-dose methotrexate, delayed intensification with vincristine, asparaginase and dexamethasone, and early use of intrathecal therapy -- treatment components that were largely established by the randomized clinical trials of major cooperative study groups[15]. As survival rates for ALL approach 100%, current research efforts have focused on improving the quality of life of patients by decreasing both acute and late morbidities, and on the development of curative treatment for the small subsets of patients who continue to develop drug-resistant leukemia, a major challenge that requires the concerted efforts of multiple pediatric oncology study groups[15].

A sobering fact of childhood ALL treatment is that very few of the advances contributing to current high cure rates are available to children who live in low- and middle-income countries (LMIC) and who account for an unacceptable proportion of cancer-related deaths[16,17]. Indeed, data from CONCORD-2, a global comparison of population-based cancer survival, showed a very wide range in survival rates for childhood ALL patients diagnosed during 2005–09, from less than 50% in several countries in Africa, Asia and South America to approximately 90% in certain countries in Europe, North America, and Oceania (Table 2)[18]. Within Asia alone, the 5-year survival estimates ranged from 34.3% to 73.1% in LMIC compared to 77.1% to 85.0% in high-income countries (HIC). Thus, a major challenge in the coming decades will be to translate the therapeutic gains achieved in HIC to clinics in LMIC. In this review, we summarize advances in the treatment and biologic understanding of childhood ALL made by international collaborative groups, provide evidence and rationales to support the study of ethnic and racial influences on ALL subtypes and treatment responses, and suggest initiatives to address the global impact of this disease.

Recent Advances from International Collaborative Studies

Differences in risk classification, age eligibility, ethnic and racial distributions, and data reporting have made it difficult to compare results among study groups to identify effective treatment components or regimens that are particularly effective for certain groups of patients. Thus, two workshops were organized to address this issue. The first, held in Memphis in 1997, provided updated results from most of the major cooperative groups, while the second, held in Ponte di Legno in 1999, produced 12 reports on the long-term outcomes of clinical trials conducted in the 1980s and 1990s, using a standard format that enabled comparison of treatment results both overall and for well-defined subgroups of patients[19]. Continued participation in these workshops by 15 major study groups has led to a second series of 15 articles summarizing the results of clinical trials conducted between 1985 and 2000[20]. The key findings of these meetings are described below and summarized in Table 3.

Clinical advances in specific subtypes of ALL

Infant ALL—Because of the rarity and poor prognosis of infant ALL, as well as its frequent co-expression of lymphoid and myeloid markers, 17 study groups collaborated to test a treatment regimen incorporating drugs that are effective against both ALL and acute myeloid leukemia. This study yielded a 4-year event-free survival (EFS) rate of 47.0%, which was superior to any previously reported result[21]. While delayed intensification failed to improve

outcome[21], allogeneic transplantation appeared to benefit the high-risk subgroup with *MLL* (*KMT2A*)-rearrangement, age less than 6 months, and either a poor response to glucocorticoids after 8 days of remission induction or a presenting leukocyte count ≥300 × 10^9/L[22].

Down syndrome ALL—Children with Down syndrome have an estimated 20-fold increased risk of developing ALL that is associated with an older age (median 5.0 vs. 4.7 years); paucity of T-cell ALL (<1% vs. 12%); a low frequency of the Philadelphia chromosome (*BCR-ABL1*) (0.7% vs. 2.4%), the t(12;21)/*ETV6-RUNX1* (8.3% vs. 25.8%), or hyperdiploidy >50 chromosomes (9% vs. 33%); and an increased cumulative risk of relapse (26% vs. 15%) and treatment-related mortality (7% vs. 2%), resulting in an inferior overall survival (74% vs. 89%) in one large collaborative study[23]. Favorable prognostic factors in that trial included younger age (<6 years), leukocyte count <10 × 10^9/L at diagnosis, and the presence of high hyperdiploidy or t(12;21)/*ETV6-RUNX1*[23]. As many as 60% of ALL patients with Down syndrome are characterized by aberrant expression of *CRLF2* (coding for cytokine receptor like factor 2), often associated with somatic activating mutations in the receptors or the downstream components of the JAK-STAT pathway[24,25], suggesting that these patients may benefit from therapy targeting JAK or one or more of its downstream pathway elements. *IKZF1* deletions occurred in approximately a third of these patients, and was associated with a particularly poor outcome[25].

ALL with induction failure—A recent collaborative study showed that 2.4% of patients treated between 1985 and 2000 had induction failure defined by morphologic evidence of ≥ 5% blasts after 4 to 6 weeks of remission-induction treatment[26]. These patients often presented with unfavorable features, including older age (median, 8.1 years), high leukocyte count (median, 42 × 10^9/L), T-cell phenotype (38%), the Philadelphia chromosome (13%), and the 11q23/*MLL* rearrangement (10%)[26]. Treatment outcome was highly variable, with hyperdiploidy >50 chromosomes and age < 6 years (without an *MLL* rearrangement) associated with a favorable prognosis in patients with B-ALL. Only patients ≥ 6 years of age with B-ALL and those with T-cell ALL appeared to benefit from allogeneic transplantation. Another recent study indicated that minimal residual disease (MRD) measurement should be used to define induction failure because some patients with an M2 marrow (5% to 25% blasts) by morphologic examination actually had MRD <0.01% and a 5-year event-free survival of 100%, whereas some patients with an M1 marrow (<5% blasts) had high MRD levels (≥5%) and a 5-year event-free survival of only 38.1%[27]. Interestingly, approximately a third of B-ALL patients with induction failure had *EBF1-PDGFRB* fusion, which responds to ABL-class tyrosine kinase inhibitors[27].

Early T-cell precursor (ETP) ALL—Based on immunophenotyping and gene expression profiling, a study identified a distinct T-cell ALL subtype (designated ETP-ALL) that was characterized by stem cell-like features, a poor early treatment response, and a high rate of induction failure and relapse[28]. Two recent studies showed that consolidation therapy with two cycles of cyclophosphamide, mercaptopurine, and cytarabine effectively reduced MRD levels in patients with ETP-ALL, resulting in an intermediate outcome (5-year EFS 86.2% and 76.7% at 3 and 5 years, respectively)[29,30].

Philadelphia chromosome-positive ALL—Philadelphia chromosome-positive ALL with *BCR-ABL1* fusion, typically found in 2% to 3% of children with ALL, was associated with a dismal outcome before the development of ABL tyrosine kinase inhibitors. In a collaborative study of 326 children and young adults treated between 1985 and 1996, the 5-year EFS rate was only 28%, and matched-related transplantation improved outcome[31]. In a second collaborative study of 610 patients treated between 1995 and 2005 without a tyrosine kinase inhibitor, the EFS had improved to 32%, and both matched-related and matched-unrelated transplantation improved outcome[32]. Subsequent studies showed that the addition of imatinib mesylate plus intensive chemotherapy improved the 5-year disease-free survival rate to 70% and could spare patients with a good initial response to remission induction from subsequent transplantation[33–35]. In a multi-center study, early achievement of a negative MRD status was associated with a superior outcome[36]. Whether second-generation ABL tyrosine kinase inhibitors, such as dasatinib[37], given in conjunction with an intensive chemotherapy backbone, can further improve outcome is being investigated.

ALL with MLL (KMT2A) rearrangement—Patients with ALL and 11q23/*MLL* (*KMT2A*) rearrangements generally have a poor prognosis[38]. However, collaborative studies have revealed considerable heterogeneity among these patients in age at presentation, type of *MLL* rearrangement, and early response to glucocorticoids[38,39]. For example, infants with t(4;11) and *MLL-AFF1* fusion had an especially dismal prognosis when they had poor early response to steroid treatment, and among patients with t(11;19) and *MLL-MLLT1* fusion, those with T-lineage ALL and age over 1 year had an excellent outcome[39]. Secondary chromosomal changes lacked prognostic impact in this subgroup[40]. With the possible exception of a small subset of infant ALL cases[22], allogeneic hematopoietic stem cell transplantation failed to improve outcome compared to chemotherapy alone[38,39]. Current clinical trials are testing molecularly targeted therapies for infant ALL with *MLL* rearrangement.

Hypodiploid ALL—Hypodiploidy <44 chromosomes has been associated with a poor prognosis; near-haploidy (24 to 31 chromosomes) and low-hypodiploidy (32 to 39 chromosomes) carry a particularly dismal outcome[41]. Near-haploid ALL is characterized by genetic alterations targeting a receptor tyrosine kinase, Ras signaling, and the lymphoid transcription factor *IKZF3*, while cases of low-hypodiploid ALL have genetic alterations in *RB1*, *IKZF2*, and *TP53*, some of which are often germline in nature[42]. In a recent single-institution study, the outcome of hypodiploid ALL was substantially improved by MRD-directed treatment, and patients with a negative MRD status at the end of remission induction were highly curable with intensive chemotherapy alone[43]. Although allogeneic transplantation is often recommended for patients with hypodiploid ALL, the efficacy of this treatment for patients with detectable MRD, especially those with a germline *TP53* mutation, remains to be evaluated.

Biologic advances: emerging subtypes of ALL

Genomic profiling studies, based on microarray-based DNA copy number and gene expression analyses and, more recently, second-generation sequencing, have advanced our

understanding of the genetic basis of leukemogenesis; identified new leukemia subtypes; and revealed genomic aberrations with diagnostic, prognostic or therapeutic implications[15,44].

Among newly identified subtypes of ALL, Philadelphia chromosome-like ALL, with a gene expression profile and a high frequency of alterations of the *IKZF1* (70% to 80%) similar to that of Philadelphia chromosome-positive ALL but lacking the BCR-ABL1 fusion protein, was characterized by resistance to daunorubicin and asparaginase, a high MRD level during remission induction, and a poor outcome[45,46,47]. A large collaborative study showed that this genotype increased in frequency from 10% among children with standard-risk ALL to 27% among adolescents and young adults with B-ALL[48]. This subtype has a complex genomic landscape, including over 30 rearrangements involving at least 13 kinase, cytokine, and cytokine-receptor genes[49]. Importantly, there are several key subgroups with therapeutic implications: (1) “ABL-class” rearrangements including *ABL1, ABL2, CSF1R, PDGFRA* and *PDGFRB* that are targetable by inhibitors of ABL1 (e.g., imatinib and dasatinib); (2) alterations activating JAK-STAT signaling including *EPOR* and *JAK2* rearrangements that are sensitive to JAK inhibitors; (3) *CRLF2* rearrangements, frequently with concomitant activating *JAK* point mutations that may also be sensitive to JAK inhibition; (4) Ras pathway mutations (*KRAS*, *NRAS*, *NF1*, *PTPN11*); and (5) infrequent targets of rearrangement including *NTRK3*, *PTK2B*, *BLNK*, and others[49–51]. Cases with a negative MRD after remission induction can be cured with low-intensity chemotherapy, those with low levels of MRD should be treated with intensive chemotherapy, while those with high levels of MRD require transplantation if they lack genetic lesions sensitive to molecularly targeted therapy[49,51].

Once considered to be a unique ALL subtype with intragenic deletions of the *ERG* gene and favorable outcome, a recent study showed that this variant occurs in up to 7% of B-ALL cases; has *DUX*-rearrangement, an early initial event in leukemogenesis; and requires gene expression or sequencing approaches for accurate diagnosis and risk assignment[50]. Rearrangements of monocyte enhancer factor 2D (*MEF2D*) and zinc finger 384 (*ZNF384*) characterize two new subtypes of B-ALL, accounting for 3.5% and 4% of B-ALL cases, respectively[44,52,53]. *MEF2D* ALL is associated with an older age at presentation (12 years), pre-B immunophenotype, poor outcome, deregulation of histone deacetylase 9 gene (*HDAC9*), and exquisite sensitivity to histone deacetylase inhibitors in xenografts, such as panobinostat[52,54]. *ZNF384* ALL is characterized by a high frequency of expression of myeloid-associated antigens (CD13, CD33) and CD10-negative phenotype, intermediate prognosis, and upregulation of JAK-STAT pathway, suggesting a potential target for therapy with a JAK inhibitor[52,53].

Recent molecular profiling studies have also shed important light on the evolutionary process of ALL during the natural history of this disease and also during ALL therapy. Backtracking studies identified sentinel genomic abnormalities (*ETV6-RUNX1*[55], hyperdiploid[56], *BCR-ABL1*[57]) in pre-leukemia blood samples at birth, strongly arguing for an in-utero origin of these initiating genomic event. This was particularly evident in studies of identical twins who share a clonotypic founding genomic aberrations early in life but one can acquire secondary somatic changes related to overt leukemia while the other twin remains healthy in the absence of additional genomic aberrations[57]. Comprehensive

profiling of these secondary events reveals ancestral relationships of ALL subclones and the evolutionary history of ALL in individual patient[58]. In ETV6-RUNX1 ALL, there is a striking over-representation of RAG-mediated genomic mutational process[59], plausibly linked to inflammation/infection-related activation of these recombination events[60]. In contrast, leukemia evolution plays a completely different role during ALL therapy, often times as a primary means of evasion of cytotoxic effects of chemotherapy[61]. Somatic mutations in key drug targets of metabolizing genes (e.g., NT5C2 and PRPS1) have been identified specifically at the time of ALL relapse and are shown to confer dramatic resistance to anti-leukemic agents[62,63,64].

Germline studies of inherited predisposition to ALL and ethnic and racial differences in disease subtypes and treatment responses

In addition to somatic genomic abnormalities in the leukemia cells of ALL patients, there is substantial genetic variation in the normal genome of the patients, mostly as inherited polymorphisms. Genome-wide association studies have shown that these germline genetic variants can influence inter-patient variability in a wide range of phenotypes[65], including susceptibility to leukemia, treatment outcome, and side effects of ALL therapy. These studies require large numbers of patients for discovery and validation, and to adjust for the ancestral composition of study cohorts; indeed, many recent advances in this field have been the result of national and, in many instances, international collaborations, especially in studies of rare ALL subtypes.

Inherited genetic determinants of leukemogenesis and treatment response— Some of the early evidence for a genetic basis of ALL susceptibility came from global comparison of the prevalence of this cancer. Epidemiologic studies had long suggested that Africans possessed a significantly lower risk of ALL development compared to Asian/Pacific Islanders and individuals of European descent, who in turn had a lower risk than individuals with Hispanic ethnicity[66–68]. These racial and ethnic groups are characterized by germline genetic variants unique to their ancestral origin[69–71]; hence, it was hypothesized that ancestry-related genetic variants might be one of the causes of racial difference in ALL risk.

In 2009, we and others took a genome-wide approach to comprehensively search for germline variants associated with susceptibility to ALL, and identified intronic single nucleotide polymorphisms within the *ARID5B*, *IKZF1*, and *CEBPE* loci as having the most robust effects on ALL risk[72]. Subsequent larger genome-wide association studies identified additional susceptibility variants in *CDKN2A*[73], *BMII-PIP4K2A*[74], and *GATA3*[75]. Interestingly, the ALL-related risk allele in *ARID5B* is unevenly distributed across populations: it is more frequent in Hispanics, followed by Europeans, and least frequent in Africans, paralleling the observed racial differences in ALL incidence (Figure 1)[76]. In fact, it was estimated that the *ARID5B* variant alone explains 30% of racial differences in ALL risk[77].

These germline risk alleles can also exhibit their effects on ALL susceptibility in an age- and leukemia subtype-specific fashion[78,79], and extend their influence to treatment outcome as well. For example, recent studies described variants in *GATA3* that were significantly

associated with the risk of developing Philadelphia chromosome-like ALL[80]. These non-coding variants in *GATA3* predisposed children to the acquisition of somatic genomic aberrations specific to Philadelphia chromosome-like ALL (e.g., *IKZF1* deletion, *CRLF2* rearrangement, and *JAK* mutations)[45,81,82]. Importantly, *GATA3* variants strongly correlated with early treatment response, as measured by MRD assay at the end of remission induction therapy, and the risk of ALL relapse across a number of different treatment regimens[80,83]. It should be noted that the *GATA3* risk alleles were significantly more common in Hispanics (particularly those with strong Native American genetic ancestry) than in European Americans[80] (Figure 1), which could contribute to the poor prognosis of ALL related to Native American genetic ancestry as we have described[84].

A number of congenital abnormalities have been linked to ALL risk[85–87], but the extent to which their associated genetic variants (e.g., chromosome 21 trisomy, variants in *ATM* and *NBN* genes associated with ataxia telangiectasia and Nijmegen breakage syndrome, respectively) influence the development and clinical behavior of ALL remains unclear. In addition to common variants with modest effects on ALL risk, there is growing evidence for rare germline genetic variants that are associated with highly penetrant familial malignancies. For example, germline loss-of-function variants in *TP53*, *PAX5*, and *ETV6* were recently discovered in multiple independent pedigrees related to recurrent ALL; further studies identified damaging variants in these key risk genes even in children without a known family history of ALL, suggesting that the genetic predisposition to ALL is more common than originally thought. In fact, comprehensive whole-genome sequencing studies have shown that up to 5% children with ALL have potential pathogenic variants in cancer-susceptibility genes[88]. This information not only will influence ALL treatment, but will also impact families through genetic counseling and testing, and will facilitate measures for cancer prevention, surveillance, and early diagnosis and treatment[89]. For example, likely-pathogenic variants in *TP53* were identified in 0.7% of children with ALL and were associated with 3.9-fold lower overall survival rate and a strikingly incidence of second cancers at 25.1%[90].

Genomic determinants of drug toxicities—ALL therapy is associated with a spectrum of acute and long-term side effects[91–93], that vary widely by treatment and genetic ancestry. For example, glucocorticoid-related osteonecrosis, which is significantly more common in patients of European descent than in those of African ancestry, was associated with inherited variations in glutamate receptor genes[94]. Asparaginase-related pancreatitis, by contrast, is associated with Native American genetic ancestry and is more frequent in Hispanics[95]; while vincristine-related peripheral neuropathy was less common in patients of African descent (possibly due to a lower frequency of the toxicity-related risk allele in the *CEP72* gene)[96] (Figure 1).

East Asians are particularly intolerant to mercaptopurine during maintenance therapy and have a high risk of hematopoietic toxicity[97]. This susceptibility is unrelated to inherited *TPMT* deficiency, a major genetic cause of mercaptopurine hematopoietic toxicity, as most individuals of East Asian descent have normal TPMT function (Figure 1). Thus, alternate hypotheses have been tested to identify the basis of mercaptopurine intolerance in this population, focusing largely on non-*TPMT* genetic polymorphisms[97,98]. A recent genome-

wide association study found that germline variants in nucleoside diphosphate–linked moiety X-type motif 15 (*NUDT15*) also strongly predisposed patients to mercaptopurine-related toxicity, during ALL therapy, independent of *TPMT*[99]. Patients homozygous for the defective allele in *NUDT15* tolerated only 6 mg/m^2/day of mercaptopurine, compared to an average of 67.5 mg/m^2/day for patients with wild-type *NUDT15*. Interestingly, the *NUDT15* risk allele was markedly common in East Asians and thus responsible for their excessive mercaptopurine toxicity[99] (Figure 1).

Global Impact of Childhood ALL

Childhood cancer and the global health agenda

Over the last two decades, the global health agenda led by the United Nations and the World Health Organization (WHO) (Table 4) has decreased the global child and adolescent mortality from 14.18 million deaths in 1990 to 7.26 million deaths in 2015,[100] with a 52% decrease in the number of deaths among children younger than five.[101] As competing causes of mortality decrease, the proportion of deaths from childhood cancer increases.[17] By conservative estimates, at least 160,000 children from 0–14 years of age are diagnosed with cancer every year, and more than 90% live in LMICs.[17] Asia accounts for half of the pediatric cancer burden, with another 25% of all expected cases arising in Africa. This geographic shift in the childhood cancer burden towards LMICs will likely continue due to the high birth rates in these countries. Due to these demographic trends, model forecasts suggest that pediatric cancer cases will increase by 30% by the end of this decade in LMICs, creating an imperative to prioritize initiatives for childhood cancer care and control.[17,102–104]

In response to this global challenge, the member states of the WHO passed a resolution on May 31, 2017, to include pediatric cancer and cancer prevention and control to the 2013–2020 global action plan.[105] As the most common and one of the most curable cancers, childhood ALL should provide an ideal model for guiding efforts to address the challenges and knowledge gaps in the WHO agenda.

Estimating the burden of childhood ALL worldwide

It is well recognized that the incidence of childhood ALL differs between high-income countries and LMICs, and also among the various ethnic and racial groups within a single country.[67,103,106–109] Table 5 compares the four major pediatric leukemia burden studies that have systematically attempted to collect cancer registration data across all global regions. Two studies relied on different methods to generate global estimates of pediatric leukemia incidence and mortality: the GLOBOCAN study[110], undertaken by the WHO International Agency for Research on Cancer (IARC), and the Global Burden of Disease (GBD) study[111] from the Institute for Health Metrics and Evaluation. Two other published estimates from the International Incidence of Childhood Cancer 2001–2010 Study (IICC-3)[109] and the CONCORD-2 study[18] report registry-specific and regional variations for pediatric leukemias as a whole and do not provide estimates for all countries in the world. Thus, the best estimate available from these sources is that more than 50,000 children are diagnosed with ALL every year across the globe.[17] In all likelihood, the number of individuals with this

diagnosis is much higher in LMICs than commonly reported. These lack of core epidemiologic data stem from multiple factors. First, epidemiologic surveys historically grouping pediatric ALL with all leukemias. Additionally, there are very few population-based pediatric cancer registries in countries with lower incomes. In 2010, the WHO estimated that population-based cancer registration were active in just 17% of low-income countries, where the cancer burden is largest.[104] Of the four major pediatric cancer disease burden estimates available, only between 3–12% of low and low-middle income country registries were included (Table 5). Finally, the accurate diagnosis of pediatric ALL remains a challenge in resource-limited settings.[112] Many of the common signs and symptoms of ALL are similar to those of common communicable diseases such as malaria and dengue, resulting in substantial number of missed diagnoses. The lack of ready access to flow cytometry and cytogenetics, making it difficult to distinguish between ALL and acute myeloid leukemia, is another factor that could contribute to under-diagnosis of this lymphoid cancer.

Treatment of Childhood ALL in Settings with Limited Resources

The ability to provide state-of-the-art curative treatments for children with cancer in LMICs is severely restricted by coexisting morbidities, as well as deficient supportive and palliative care, among other factors,[17] as indicated by the lagging survival estimates (Table 2). The direct translation of effective protocols from developed countries to settings in LMICs is not a realistic option, so that steps must be taken to overcome inadequate health care capacities, socioeconomic limitations, and cultural barriers. Tiered system approaches have been proposed, with glucocorticoids plus two or three-drug induction regimens recommended according to local needs and the ability to deliver supportive care[113,114]. Early deaths due to infection, bleeding, and treatment abandonment often exceed the total cumulative frequency of relapse. Indeed, treatment refusal and abandonment may involve as many as 50–60% of children in some regions, thus often exceeding all other causes of treatment failure.[115] Most of these patients withdraw from protocols early, usually soon after induction remission.[116] An integrated multi-disciplinary approach that addresses abandonment comprehensively and that prioritizes family education and support is key to the success of any strategy. Hence, treatment strategies should be devised with clearly defined goals and trade-offs in mind. Modifications of the selected regimens should be driven by periodic review of local outcomes and should proceed as stepwise increments in diagnostic and stratification complexity, and in state-of-the-art treatment[7,9,114,117–119]. For example, while the Inter-Continental BFM-2002 study, conducted in 15 upper-middle and high-income countries on three continents produced 5-year event-free survival and overall survival rates of 74% and 82%, respectively,[7] the adaptation of this regimen in lower-middle income countries in Central America resulted in 20% lower survival rates.[118,119] The suboptimal results were not only due to delayed diagnosis, early death, and treatment abandonment, but also increased relapse rates reflecting in part a higher frequency of CNS leukemia and unfavorable genetic subtypes (e.g., *BCR-ABL1* fusions) and lower frequency of favorable genetic subtypes (e.g., *ETV6-RUNX1* fusions)[119].

Thus, differences in outcome by ethnic group traditionally attributed to quality of care may need to be reassessed as better biologic disease characterization is performed and genome-

wide studies are conducted. A recent U.S. study of more than 2,000 children with ALL identified 302 germline SNPs associated with relapse after adjusting for treatment and ancestry and 715 additional SNPs associated with relapse in an ancestry-specific manner.[120] Therefore, it is critical to incorporate ancestry considerations into the development of global strategies and the implementation of adapted regimens. Finally, event-free survival should be analyzed in two ways, by treating abandonment as an adverse event and by censoring cases at the time of abandonment; these two estimates will reflect the upper and lower bounds of the true event-free survival estimate.[121]

The judicious adaptation of established diagnostic and therapeutic guidelines to local settings and the proper allocation of resources requires a well-trained and specialized healthcare workforce; the importance of investing in training and education while stepping up in diagnostic and treatment complexity cannot be underestimated. Models of successful implementation of training programs through partnerships with institutions in high-income countries have been well described.[106] The application of cost-effective interventions and adjusting new technologies to local technical capacity should also be prioritized. Examples include the use of simplified and inexpensive assays for MRD that do not require extensive prior training in leukemia and allow for the use of risk-adapted treatment,[122,123] or the implementation of early warning score systems to decrease hospital mortality in this vulnerable population.[124]

Delivering care: essential medicines for childhood ALL and cost of treatment

In 2004, the Ponte di Legno Working Group issued a statement on the right of children to have full access to essential treatment for ALL. This stance has prompted international agencies and regulatory authorities to provide the necessary antileukemic drugs at affordable costs worldwide, to support the development of centers of excellence, and to encourage authorities in LMICs to support measures that could increase the chances of a child to achieve cure of ALL[125]. Initiatives such as this will gain in importance if recent shortages in cancer drug availability persist.

Essential medicines—The WHO curates essential medicines lists to help countries prioritize and select the medicines to include in their national medication formularies and national reimbursable medicines lists -- a model that guides purchasing patterns for many governmental agencies, non-governmental organizations, and charities.[126] In 2007, the WHO launched a parallel essential medicines list for children, including an expanded list of chemotherapeutic agents that has been updated every 2 years[127]. In 2015, the expert committee of the WHO undertook a comprehensive review of essential medicines for cancer, in both adults and children, as part of an international consultative process coordinated by the Union for International Cancer Control. This resulted in a comprehensive review of treatments for 29 cancer indications and a request to add 21 cytotoxic medicines and one supportive therapy[128]. Despite these efforts, there is considerable variation in the listing of anti-cancer medicines by geographical region, socioeconomic status, and burden of disease, with low-income and African countries showing more restrictions.[126,128] The impact of these changes on the listing of ALL drugs cannot be ignored, as the lists often determine national access. In a global review of national essential medicines, the authors noted major

deficiencies in ALL drugs[128]. While methotrexate and vincristine were included in 95% and 82% of the national lists, respectively, mercaptopurine, L-asparaginase, daunorubicin, and imatinib were included in only 64%, 50%, 41%, and 30%,[128] further highlighting the need for coordinated efforts that include all stakeholders and prioritize the pediatric oncology needs. However, inclusion of childhood ALL drugs in national essential medicines lists is meaningless without a strong commitment by governments to guarantee access.

Access to medications for patients with cancer in LMIC is the subject of a recent review.[129] The authors observed that "in low-resource settings, institutions might be weaker and problems with management and accountability might be prevalent, leading to corruption and perverse incentives that result in underfunding of and misallocations of expenditures". These problems may be compounded by inappropriate utilization and poor inventory control.[130] Solutions include the establishment of universal insurance coverage that empowers consumers,[129] and the use of generic and bio-similar off-patent medications, especially if produced in LMIC and utilizing compulsory licensing as authorized by the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement negotiated by the World Trade Organization.[131,132] Access may be enhanced also by participation in clinical trials, especially if funded by the pharmaceutical industry.[129]

Treatment costs—Costs of cancer treatment are rising so rapidly that even wealthy countries face economic difficulty in delivering high-quality cancer care equally to all of their citizens.[104] The frailty of the healthcare systems in LMICs adds to their lack of essential resources; indeed, most have evolved into fragmented structures that provide only minimum urgent care. Further, the lack of health-care coverage for large segments of the population exposes them to a high risk of catastrophic and impoverishing health payments, which drives many families into poverty. In 2008, for example, one-third of the population in Latin America was at high risk for such impoverishment due to catastrophic health expenditures.[133]

Very few data exist regarding the cost of treating childhood cancer in LMIC. Two recent studies using a threshold analysis and global costing procedure suggest treating childhood cancers in LMICs is very cost-effective as per WHO criteria.[134,135] Very few formal micro-costing studies of ALL specifically have been completed with published reports showing a wide variation in ALL treatment costs, ranging from $3,000 in Bangladesh[136] to $10,000 to 20,000 in Brazil[134], Mexico[137], and China[138,139] to $100,000 in North America and Europe[140]. A significant proportion of the costs (up to 50% in many cases) are associated with diagnostics, supportive care, and hospitalization. While access to chemotherapeutic agents is a limiting factor in many occasions, the costs related to drugs (including chemotherapy and supportive care drugs) accounts for less than one-third of the total costs[135]. In low-income countries, the monthly expenses related to the treatment of a child with ALL can be more than seven times the monthly per capita income, resulting in a dramatic loss of income and employment.[141] The high price of some drugs for the treatment of cancer and supportive care are all-too-often a major obstacle to the provision of appropriate treatment for children with ALL in LMICs, higher than in HIC relative to family income, and yet treatment of childhood ALL is demonstrably very cost-effective[134]. Indeed the Institute of Medicine has identified the treatment of highly curable cancers in young

people as one of the three main strategies to address the global cancer crisis[142]. The precedents offered by GAVI, the Global Fund and UNITAID suggest that an innovative financing approach, based on a value chain framework,[143] is worthy of exploration.

An example of the coordinated efforts by multiple stakeholders to secure treatment for children with ALL is afforded by China, where 10,000 to 12,000 children are diagnosed with ALL every year. In the past few decades, China has moved from a system of universal insurance to a largely privatized health-care system with the majority of rural residents remaining uninsured[144]. In December 2004, a standardized, cost-efficient protocol was developed jointly by the Shanghai Children's Medical Center, the Beijing Children's Hospital, and St. Jude Children's Research Hospital to treat underprivileged children with low- and intermediate-risk ALL with the support of a charitable foundation. In 2009, the effectiveness and the affordability (&14,000 USD) of the clinical trial were reported[138], which prompted the Ministry of Health in 2010 to provide governmental funding toward the treatment of children with ALL[145]. With this drastic increase in the number of patients having access to treatment and the unprecedented opportunity of clinical and translational research, Shanghai Children's Medical Center and St. Jude Children's Research Hospital in October 2014 formed a national childhood ALL study group comprising 20 major hospitals and medical centers across China. A risk-adapted treatment protocol was initiated in early 2015 with a targeted enrollment of 1,200 patients a year.

Collaborative Efforts and Network Development

International partnerships that integrate twinning between institutions in HIC and LMIC along with commitment from local governments and participation of global health agencies, advocacy groups, and local foundations, have provided successful models for building sustainable pediatric oncology programs in LMIC.[106] The incorporation of the research methodology is a necessary step in their growth and in the regional initiatives that eventually may result; cooperative groups have been formed in different resource-limited regions of the Americas, Africa, East Mediterranean, Asia, and Oceania[17]. These partnerships can help design and conduct clinical research focused on the epidemiologic, biologic, clinical, and psychosocial questions relevant to the advancement of local care, the development of treatment guidelines and interventions, and to guiding public health priorities.[17,146] The importance of incorporating a clinical research infrastructure early in the process of program building should be emphasized, and cost-effective data management tools should be developed. Ultimately, strengthening those networks and facilitating the development of new regional collaborations with support from larger consortia in high-income countries has the potential to create a new framework to advance care for children with ALL and other malignancies worldwide. Different levels of consortia with a step-wise increment in their level of complexity and range of initiatives developed have been proposed[17].

Conclusions and Future Directions

Collaborative studies have refined the molecular diagnosis, improved risk assignment, validated new treatment strategies, and contributed to personalized therapy by identifying new targets for therapeutic intervention. In many instances, it has been possible to translate

these advances to patients in LMIC. For example, the finding that systemic or intrathecal chemotherapy delivered effectively can safely replace prophylactic cranial irradiation[147], and the development of simple and inexpensive assays to measure MRD levels during early remission induction to identify low-risk patients for reduced-intensity therapy, could be readily applied to the treatment of patients in limited-resource settings[122]. That a single year of chemotherapy cured two thirds of patients with newly diagnosed ALL, especially those with *ETV6-RUNX1*[148], and that a single infusion of chimeric antigen receptor-engineered T-cells could be curative in patients with relapsed or refractory ALL[149], are particularly encouraging. It is hope that such treatment strategies can eventually be applied to patients in LMIC to avoid the need of long-term continuation treatment.

Global comparison of ALL-related traits can often shed new light on the biology of leukemia as well as treatment toxicities. To this end, international efforts are under way to systematically map treatment-related toxicities across diverse regions to develop adapted guidelines and support related research initiatives[150]. Perhaps the greatest challenge for the future will stem from rapid demographic changes, which place even greater emphasis on devising ALL management strategies that can be rapidly employed in the face of large shifts in patient populations. Thus, there is a need for high-quality research that incorporates comprehensive epidemiologic studies and explores feasible, evidence-based, cost-effective, and resource-adapted therapies[151]. At the same time, efforts should be intensified to understand how inherited genetic polymorphisms underlie ethnic and racial differences in the incidence and outcome of ALL, and how the acquisitions of key somatic mutations could be blocked to lower the risk of ALL development[15], the Holy Grail for pediatric oncologists. It will require a coordinated effort by academic institutions, global and public health governmental and non-governmental agencies, advocacy groups, and professional societies to address the global challenge of childhood ALL. Specific goals to guarantee access to care and to provide adequate diagnosis and treatment to all children with ALL within the next decade should be set, and the firm objective to cure all children, regardless of where they live, should concentrate all our efforts.

Search strategy and selection criteria

We searched PubMed for English-language articles published from Jan 1, 2000 to November 1, 2017, with the keywords “acute lymphoblastic leukemia”, “acute lymphocytic leukemia”, “acute lymphoid leukemia”, “pediatric”, and “childhood”. Further relevant articles were selected from the lists used in our previous publications. In some instances, review articles were selected over original articles because of space constraints.

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Key messages

- More accurate diagnosis, improved risk-directed chemotherapy, and advances in supportive care have made childhood acute lymphoblastic leukemia (ALL) one of the most curable cancers. However, the 5-year survival rates of over 90% being achieved in most developed countries do not extend to countries with limited resources.
- Factors contributing to the inferior outcomes in low-income countries include delayed diagnosis, treatment abandonment, increased numbers of infectious deaths and increased relapse rate due to a high proportion of patients with unfavorable genetic subtypes of ALL and a lack of access to effective treatment.
- Inherited genetic variants influence the susceptibility to ALL, treatment response, and the side effects of therapy, and merit greater attention as means to reduce the global disparities in ALL.
- Emerging ALL subtypes mandate research to devise effective targeted therapies for these disease variants and integrate them into frontline treatments.
- Advancing the cure rates and quality of life of childhood cancer patients in low- and middle-income countries will require greater involvement by international organizations, both governmental and non-governmental.

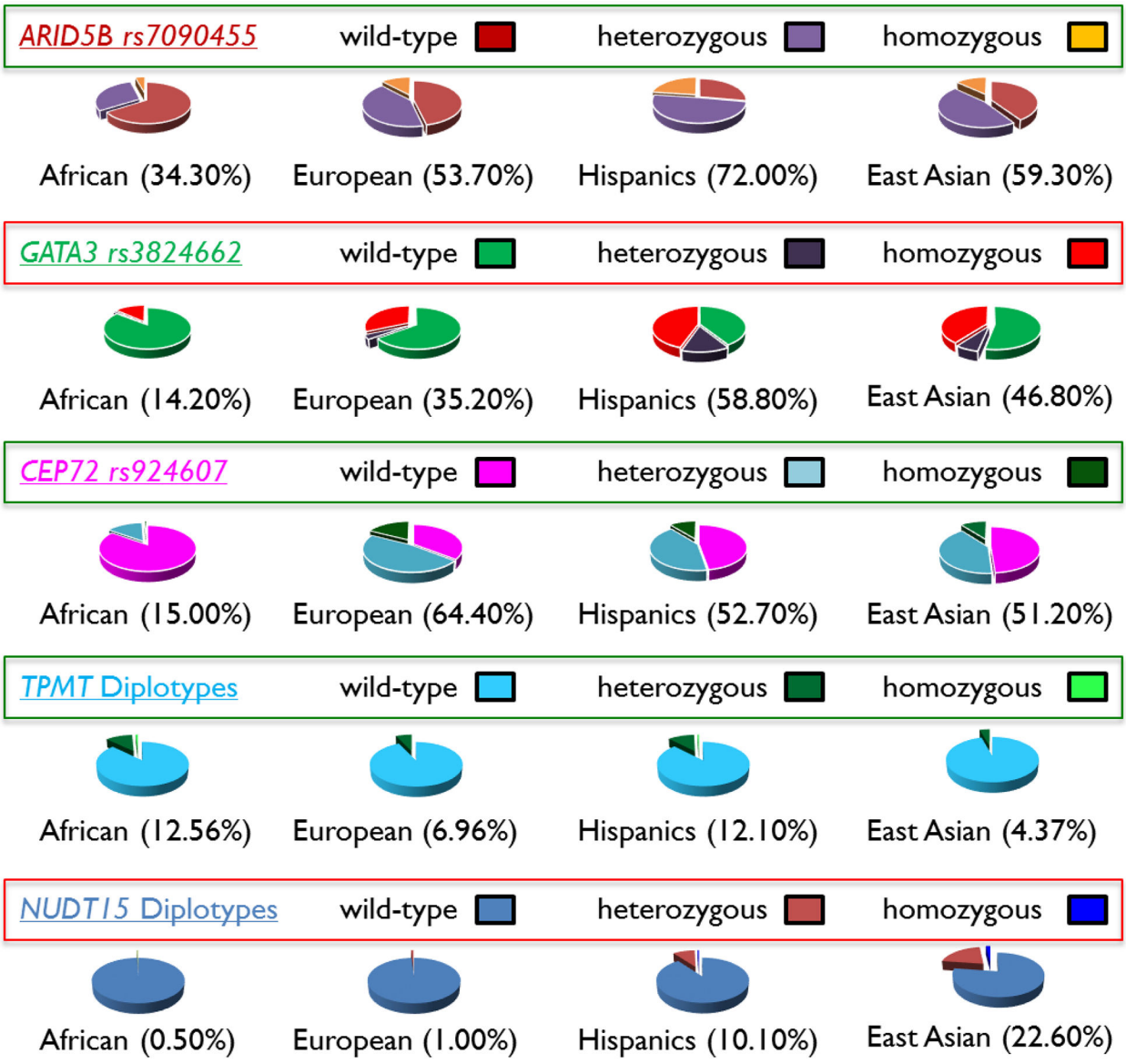

Figure 1. Global variation in the frequency of key genetic variants associated with ALL susceptibility and treatment toxicities.

Numbers in parentheses denote the percentage of individuals with the risk allele.

Table 1.

Patient characteristics and treatment results from selected clinical trials

Study group	Years of study	No. of patients	Age range (years)	T-cell ALL (%)	5-year cumulative rate of any relapse (%)	5-year EFS (%)	5-year survival (%)	Data source
AIEOP-BFM 2000	2000–2006	4,839	1–17	13.2	13.2	81.4±0.6	91.9±0.4	Moricke et al.[2]
CoALL-07–03	2003–2010	743	1–18	12.9	NA	83±0.3	NA	Escherich et al.[3]
COG	2000–2005	7,153	0–21	7	7.22	NA	90.4±0.5	Hunger et al.[4]
DCOG-10	2004–2012	778	1–18	14.2	8.3	87±1.2	91.9±1.0	Pieters et al.[5]
DFCI 05–001	2005–2010	551	1–18	13	8.96	85	91	Place et al.[6]
EORTC 58951	1998–2008	1947	1–18	15.2	14.7	82.6±0.9	89.7±0.7	Domenech et al.[7]
IC-BFM 2002	2002–2007	5,060	1–18	13.3	19	74±1	82±1	Stary et al.[8]
JCCLSG ALL 2000	2000–2004	305	1–15	9.8	17	79.7±2.4	89.2±1.8	Yamaji et al.[9]
Ma-Spore ALL 2003	2002–2011	556	0–18	8.8	NA	80.6±3.5	89.2±2.7	Yeoh et al.[10]
MRC UKALL 2003	2003–2011	3,126	1–25	12	8.8	87.3±1.4	91.6±1.2	Vora et al.[11]
NOPHO-2008	2008–2014	1,022 266	1–9 10–17	9.1 25.2	10 3±1	89±1 80±3	 1 2 ±± 47 98	Toft et al.[12]
SJCRH XV	2000–2007	498	1–18	15	9.3	87.3±2.9	93.5±1.9	Pui et al.[13]
TPOG	1999–2010	152	0–18	7.2	NA	84.2±3.0	90.2±2.4	Liu et al.[14]

Abbreviations: ALL, acute lymphoblastic leukemia; AIEOP, Associazione Italiana di Ematologia Pediatrica Group; BFM, Berlin-Frankfurt-Münster; CNS, central nervous system; CoALL, Cooperative ALL Study Group; COG, Children's Oncology Group; DCOG, Dutch Children's Oncology Group; DFCI, Dana-Farber Cancer Institute consortium; EFS, event-free survival; EORTC – CLG, European Organisation for Research and Treatment of Cancer - Children Leukemia Group; IC-BFM, Intercontinental-BFM; JCCLSG, Japanese Children's Cancer and Leukemia Study Group; Ma-Spore, Malaysia-Singapore; MRC UKALL, Medical Research Council United Kingdom acute lymphoblastic leukemia; NA, not available; NOPHO, Nordic Society of Pediatric Hematology and Oncology; SJCRH, St. Jude Children's Research Hospital; TPOG, Taiwan Pediatric Oncology Group.

Table 2.

5-year survival for children (aged 0 to 14 years) diagnosed with acute lymphoblastic leukemia between 2005 and 2009 by continent and country.

	% Survival estimate (95% CI)
Africa	
Algeria registries	54.1 (31.3 – 76.8) *
Lesotho †	39.5 (16.4 – 62.7)
Libya (Benghazi)	70.1 (43.4 – 96.9)
Tunisia (Central)	50.1 (26.0 – 74.2) *
America (Central and South)	
Argentina registries †	66.9 (64.4 – 69.3)
Brazilian registries	65.8 (57.7 – 74.0)
Chilean registries	66.4 (51.3 – 81.5)
Colombian registries	53.8 (43.9 – 63.6)
Ecuadorian registries	62.6 (53.7 – 71.6)
Puerto Rico †	80.1 (71.1 – 89.0)
America (North)	
Canada †	90.6 (88.6 – 92.7)
US registries	87.7 (86.9 – 88.4)
Asia	
Chinese registries	61.1 (51.3 – 70.8)
Cyprus †	83.2 (69.7 – 96.7)
Indian registries	64.7 (50.1 – 79.2)
Indonesia (Jakarta)	44.3 (13.4 – 75.3)
Israel †	85.0 (80.5 – 89.4)
Japanese registries	81.1 (76.8 – 85.4)
Jordan †	16.4 (6.8 – 26.0) *
South Korea †	77.1 (74.7 – 79.5)
Malaysia (Penang)	69.4 (57.4 – 81.5)
Mongolia †	34.3 (11.9 – 56.8)
Taiwan †	77.9 (74.5 – 81.3)
Thai registries	55.1 (45.5 – 64.6)
Turkey (Izmir)	73.1 (66.1 – 80.2)
Europe	
Austria †	91.1 (86.9 – 95.2)
Belarus †	88.3 (83.6 – 93.0)
Belgium †	89.7 (86.1 – 93.3)
Bulgaria †	71.0 (64.2 – 77.7)
Croatia †	85.9 (80.0 – 91.8)

	% Survival estimate (95% CI)
Denmark†	87.2 (81.5 – 92.9)
Estonia†	62.6 (52.0 – 73.3)
Finland†	81.9 (75.3 – 88.5)
French registries†	89.2 (87.7 – 90.8)
German registries	91.8 (89.8 – 93.7)
Iceland†	84.1 (70.0 – 98.3)
Ireland†	85.3 (79.1 – 91.5)
Italian	87.7 (84.9 – 90.5)
Latvia†	75.0 (64.3 – 85.8)
Lithuania†	69.6 (59.1 – 80.1)
Malta†	72.5 (59.5 – 85.4)
Netherland†	85.9 (82.7 – 89.2)
Norway†	89.7 (84.4 – 94.9)
Portugal†	86.8 (80.7 – 92.9)
Slovakia†	78.2 (69.5 – 87.0)
Slovenia†	75.7 (63.8 – 87.6)
Spanish registries†	83.3 (79.1 – 87.4)
Sweden†	85.5 (80.9 – 90.1)
Swiss registries†	88.4 (83.8 – 93.0)
UK†	89.1 (87.6 – 90.7)
Oceania	
Australian registries	88.6 (85.9 – 91.4)
New Zealand†	89.3 (83.8 – 94.8)

*Survival estimate considered less reliable.

†100% coverage of the national population.

Data extracted from Allemani et al.[18]

Table 3.

Clinical Research Findings from Selected Collaborative Studies (I will revise this table)

Subgroup of ALL	Years of Study	No. of Study groups	No. of Patients	Major Findings	References
Infant ALL	1995–2005	17	482	Hybrid treatment regimen with drugs against both ALL and acute myeloid leukemia improved outcome. Transplantation benefited high-risk subgroup with *MLL* rearrangement, age < 6 months, and poor early steroid response or hyperleukocytosis.	Pieters et al[21] Mann et al.[22]
Down syndrome	1995–2004	16	653	These patients have increased risk of relapse and treatment-related mortality. More than half of the cases are characterized by aberrant expression of CRLF2, often associated with JAK-STAT activation.	Buitenkamp et al.[23,25] Mullighan et al.[24]
Induction failure	1985–2000	14	1041	Treatment outcome for patients with induction failure was highly heterogeneous. Only patients >6 years with B-ALL and those with T-cell ALL appeared to benefit from allogeneic transplantation.	Schrappe et al.[26]
Early T-cell precursor	1992–2006	2	30	These patients have distinctive immunophenotype ($CD1a^{-}$, $CD8^{-}$, $CD5^{weak}$ with stem-cell or myeloid markers) and high levels of minimal residual disease after remission induction.	Coustan-Smith et al.[28]
Philadelphia chromosome-positive	1986–1996	10	326	Older age, high presenting leukocyte count, and poor steroid response adversely affected treatment outcome.	Arico et al.[31]
	1995–2005	10	610	Both matched-related and matched-unrelated transplantation improved treatment outcome.	Arico et al.[32]
	2004–2009	10	178	Imatinib combined with intensive chemotherapy was well tolerated and might improve outcome.	Biondi et al.[33]
Philadelphia chromosome-like	2008–2009	2	221	Genetic alteration of *IKZF1* was associated with high levels of minimal residual disease and a poor prognosis.	Mullighan et al.[45]
	2008–2009	2	297	These cases had frequent deletions of genes involved in B-cell development, resistance to asparaginase and daunorubicin, and poor outcome.	Den Boer et al.[46]
	2014	5	264	Over 90% of the cases have kinase activating alterations, some amenable to inhibition with tyrosine kinase inhibitors.	Roberts et al.[48,49]
MLL-rearranged	1983–1995	11	497	Prognosis varied according to the age of presentation, type of *MLL* rearrangement and early steroid treatment response; allogeneic transplantation in general did not improve outcome.	Pui et al.[38,39]
	1983–1995	12	450	Secondary chromosomal abnormalities have no prognostic significance in patients with 11q23 rearrangements.	Moorman et al.[40]
Hypodiploid<44 chromosomes	1986–1996	11	139	Prognosis was poor, especially among patients with near-haploid or low-hypodiploid ALL.	Nachman et al.[41]
	2008–2013	2	126	Near-haploid cases have genetic alterations targeting receptor tyrosine kinase and Ras pathway and *IKZF3* mutations, and low-hypodiploid cases are characterized by *IKZF2* alterations and *TP53* mutations, half of which are inherited.	Holmfeldt et al.[42]

Table 4.

Timeline of global health agenda related to childhood health and childhood cancer

September 2000	**United Nations Millennium Development Goals**	
	MDG4: To reduce under-five mortality rates by two thirds by 2015	
September 2011	**United Nations General Assembly**	
	Resolution 66/2: Political Declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-Communicable Diseases	
May 2013	**World Health Assembly**	
	Resolution 66/10: Follow-up to the Political Declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-Communicable Diseases	
		WHO Global Action Plan for NCD - 25% reduction in NCD mortality by 2025
January 2016	**United Nations Sustainable Development Goals**	
	SDG3: To ensure healthy lives and promote well-being for all at all ages	
	SDG3.2	By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births.
	SDG3.4	By 2030, reduce by one-third premature mortality from NCD through prevention and treatment and promote mental health and well-being.
	SDG3.8	Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all.
May 2017	**World Health Assembly**	
	Resolution 70.12: Cancer Prevention and Control in the Context of an Integrated Approach	

Table 5:

Comparison of Current Global Pediatric Leukemia Burden Studies

	GBD 2015	GLOBOCAN 2012	IICC-3	CONCORD-2
Global Estimates	Yes	Yes	No	No
Number of Registries Included	562	290	153	215
From Low and Low Middle Income Countries*	12%	7%	11%	3%
Outcomes Estimated	Incidence, Mortality, Disability Adjusted Life Years	Incidence, Mortality	Incidence	Survival
Global Annual Leukemia Incidence	73,549	49,752	Not Estimated	Not Estimated
ALL specific	50,732	Not Estimated	Not Estimated	Not Estimated
Global Annual Leukemia Mortality	36,738	27,775	Not Estimated	Not Estimated
ALL specific	24,690	Not Estimated	Not Estimated	Not Estimated
Disability Adjusted Life Years (ALL specific)	1,997,861	Not Estimated	Not Estimated	Not Estimated

*Based on 2017 World Bank LMIC Status