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Therapies on the Horizon for Childhood Acute Lymphoblastic Leukemia

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Abstract

Purpose of the review—The prognosis for children with the most common childhood malignancy, acute lymphoblastic leukemia (ALL) has improved dramatically. However the burden of therapy can be substantial with long term side effects and certain subgroups continue to have a poor outcome.

Recent Advances—The recent discovery of new genetic alterations in high risk subsets provide targets for precision medicine-based interventions using existing FDA approved agents. Novel immunotherapeutic approaches are being deployed in relapsed ALL, one of the leading causes of cancer cell death in children. Moreover genomic analysis has charted the evolution of tumor subclones and relapse specific alterations now provide a mechanistic explanation for drug resistance setting the stage for targeted therapy. There is greater recognition that host factors, genetic polymorphisms, influence cancer risk, response to therapy and toxicity. In the future it is anticipated that they will be integrated into clinical decision making to maximize cure and minimize side effects. Recent efforts to limit prophylactic central nervous system irradiation have been successful thereby sparing many children late neurocognitive impairments.

Summary—Integration of advances in precision medicine approaches and novel agents will continue to increase the cure rate and decrease the burden of therapy for childhood ALL.

Keywords

acute lymphoblastic leukemia; Ph-like ALL; tyrosine kinase inhibitors; clonal evolution; genetic polymorphisms; CNS irradiation

Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosed each year in the United States and Western Europe. Fifty years ago, very few children with ALL survived.

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Today the 5-year survival rate exceeds 90% (1). The remarkable survival improvements have been driven by the use of complex multiagent chemotherapy regimens, focused central nervous system (CNS) treatment, and recognition of clinical, biological, and treatment response characteristics that identify patients at lower or higher risk of treatment failure. Despite these successes, most children with ALL who relapse will not be cured, and ALL remains a leading cause of cancer death in young persons. More recently, precision medicine approaches have been incorporated into small ALL subsets and large scale next generation sequencing (NGS) strategies have identified additional genetic alterations and pathways for precision medicine targeting. Below we discuss new therapeutic approaches with the goal of curing every child and teenager with ALL that allows them to lead happy, productive lives.

Integration of precision medicine approaches into ALL treatment

The remarkable advances that have occurred over the past fifty years are due primarily to optimizing use of the same basic “tool kit” of chemotherapy agents. The major exception is those children with Ph⁺ ALL. The Ph⁺ or (9;22)(q34;q11) translocation fuses the chromosome 22 gene *BCR* to the *ABL1* gene from chromosome 9 and encodes for a BCR-ABL1 fusion protein that is constitutively active tyrosine kinase driving cell growth and promoting survival. The Ph⁺ is present in essentially all patients with chronic myeloid leukemia (CML), about a quarter of adults and about 3–5% of children with ALL. Prior to the development of tyrosine kinase inhibitors (TKIs), Ph⁺ ALL was a very poor prognosis subset with long-term event-free survival (EFS; survival without relapse or death from toxicity) rates of only about 35% despite widespread use of allogeneic hematopoietic stem cell transplantation (HSCT) (2).

Imatinib was the first BCR-ABL1 specific TKI and showed remarkable activity in patients with CML. Studies then showed that addition of imatinib to intensive chemotherapy in children with Ph⁺ ALL substantially improved outcome (3). In the original Children’s Oncology Group (COG) AALL0031 trial, the 7-year EFS rate for children with Ph⁺ ALL treated with this strategy was 72%, as compared to 27% for similar children treated in the pre-TKI era (4).

This approach is now termed precision cancer medicine where targeted agents are directed against underlying molecular defects that drive the survival of cancer cells. In pediatric ALL, the TARGET Project (Therapeutically Applicable Research to Generate Effective Therapies; <https://ocg.cancer.gov/programs/target>) has uncovered many previously unknown somatic genetic abnormalities critical for the growth of leukemia cells. One of the most important subtypes is called “Philadelphia chromosome-like” (Ph-like) or BCR-ABL1-like ALL because these cases have gene expression profiles that resemble those of Ph⁺ ALL, but lack BCR-ABL1 fusion (5, 6).

The Ph-like ALL subtype, which accounts for about 15% of pediatric ALL cases and 25% of ALL cases arising in older teenagers and young adults, is associated with a very poor outcome reminiscent of that of Ph⁺ ALL in the pre-TKI era. A number of studies have now unraveled the complex genomics of Ph-like ALL and shown that there are several subgroups that comprise this disorder. Importantly several subgroups are defined by genetic lesions that

are targetable by FDA-approved available TKIs (7). One subgroup which accounts for about 25% of Ph-like ALL cases, is defined by translocations and genomic rearrangements that create fusion genes analogous to BCR-ABL1 involving one of four tyrosine kinase genes, *ABL1* itself, its homologue *ABL2*, *CSF1R*, or *PDGFRB*. These kinases are fused in-frame to a wide variety of partner genes creating constitutively active tyrosine kinases like BCR-ABL1 and all are sensitive to imatinib and related ABL class TKIs, just like BCR-ABL1. There are a variety of anecdotal reports showing that children and adults with Ph-like ALL respond remarkably to imatinib or dasatinib. The COG is developing a clinical trial that will open in 2016 and will treat children with Ph-like ALL and ABL class fusions with chemotherapy plus dasatinib.

A second major class of Ph-like ALL has driver genetic lesions that affect the JAK (Janus kinase) signaling pathway, which can be targeted by ruxolitinib. The COG is developing a 2nd trial, also expected to open to accrual in 2016, to add ruxolitinib to chemotherapy in this subtype of Ph-like ALL. It is hoped that NGS studies will define other subtypes of ALL and other pediatric cancers that can be treated with analogous precision medicine approaches.

Improved prevention of relapse and treatment of relapsed ALL

The outcome for children who relapse, especially those who relapse in the bone marrow, remains dismal making relapsed ALL the fifth most common childhood malignancy and one of the most frequent causes of cancer related mortality in children (8). In spite of many attempts to intensify therapy including using HSCT, the outcome for relapsed ALL has not improved over the last two decades creating an urgent need for novel approaches to prevent and treat relapse.

Currently all patients undergo re-induction chemotherapy even those with isolated extramedullary relapse since these patients will develop systemic disease if not re-treated. Those with early relapse benefit from HSCT. However many patients fail to achieve remission, suffer a second relapse early before HSCT and/or may not have a suitable donor. Even those patients who do undergo HSCT remain at significant risk for second relapse. Current strategies use early response to re-induction therapy to determine which of the children with late relapse should undergo HSCT and which should be treated with chemotherapy alone (8).

Given the poor outcome of patients retreated with conventional agents with or without HSCT new approaches are mandatory. Two new immunologically based therapies offer great promise. Many studies have shown that cytotoxic T cells usually present within tumors play a critical role in tumor surveillance yet cancer cells develop mechanisms to evade immune attack. Blinatumomab is a bi-specific T cell engager (BiTE) single chain antibody with specificity for T cells (CD3) and leukemia cells (CD19) (9, 10). As such it acts to bring T cells in close proximity to the malignant B cells initiating an immune synapse and subsequent cytotoxicity (Figure 1). Blinatumomab has shown impressive responses in patients with B-cell malignancies that resulted in the FDA granting breakthrough status in December 2014 (11–13). The drug is given by continuous infusion for 28-day cycles and in a phase I/II trial in children with relapsed refractory disease 32% of patients achieved a complete

response (14). Common side effects included fever, nausea and headache. A rare but very serious side effect is cytokine release syndrome (CRS) initiating by a vigorous immune response. Such patients can develop hypotension, severe capillary leak and multisystem organ failure. Blinatumomab is presently being evaluated when delivered with conventional agents in a COG trial for relapsed ALL.

Another particularly exciting approach is the use of CD-19 directed chimeric antigen receptor (CAR) T cells (15) (Figure 1). CARs contain an extracellular tumor recognition domain, in this case a single chain monoclonal CD19 antibody fragment, linked to an intracellular T cell activation module. A variety of gene transfer techniques can be used to engineer the patient's own harvested T cells to express this protein and the autologous T cells are then re-infused back into the patient. Early CAR T cells relied on an intracellular CD3 signaling domain but second and third generation versions have added one and two co-stimulatory domains. These changes led to greater stimulation and persistence of engineered T cells. Clinical trials of CD-19 CAR T cells have shown striking activity in both adult and pediatric ALL with complete response rates from 70% to 90% in relapsed/refractory cases (16, 17). While such patients have proceeded to HSCT many have achieved sustained responses with CAR T cells alone. CRS is much more common (and severe) with CAR T cells and represents dramatic T cell proliferation and cytokine production. It is more likely to occur in patients with high tumor burden and most patients require intensive care level support. The impact of CRS has been reduced significantly by the use of the interleukin-6 receptor inhibitor tocilizumab without reducing the efficacy of CAR T cells (18). While these results are impressive challenges remain in terms of optimizing CAR T cell therapy. Relapse after CAR T cells has been associated with the emergence of both CD-19 positive and negative leukemia cells. In the former case efforts to improve persistence of CAR T cells is needed. In the latter case the use of "tandem" CAR T cells targeted to additional leukemia cell surface molecules may prevent the emergence of such escape variants.

Until recently the underlying biological mechanisms that lead to drug resistance and relapse were unknown. High throughput genomic analysis of diagnosis/relapse paired samples showed that the relapse clone is almost always related to the clone at initial diagnosis. In fact both the leukemia population at diagnosis and relapse is made up of many related subclones containing unique changes but sharing common lesions. (19). The relapse is usually generated from a progenitor clone or emerges from expansion of a minor subclone at diagnosis through the evolutionary pressure of chemotherapy (Figure 2) (20, 21). Specific alterations are associated with pan-resistance to all conventional agents or may be associated with resistance to a single class (22). For example activation of both the Wnt and mitogen activated protein kinase pathways (MAPK) is commonly observed at relapse and is associated with resistance to all agents used in therapy (23, 24). *Ras* mutations in part drive MAPK activation and targeted agents are available that are attractive candidates for novel therapy (24, 25). The most common relapse specific mutations cluster in the *NT5C2* gene that encodes a 5' nucleotidase (26, 27). These mutations activate the enzyme to block the action of purine analogues (6-mercaptopurine (6-MP) and 6-thioguanine (6-TG)) by preventing conversion of the pro-drug into the active products. 6-MP is the cornerstone of maintenance therapy. Likewise recently mutations have been noted in another enzyme PRPS1

that also blocks the pathway needed for pro-drug activation of purine analogues although it does so through an alternative mechanism and inhibitors of the de novo purine biosynthetic pathway may overcome resistance induced by *PRPS1* mutations (28). In both cases these mutations are observed in patients who relapse early and carry the worst prognosis

Understanding host differences in treatment response and toxicity

The human genome contains 3.2 billion base pairs and while the great majority of humans are > 99% identical to one another subtle variation does exist. The majority of these differences are single base substitutions called polymorphisms (SNPs). In addition to SNPs small insertions/deletions (“indels”) or large structural variations differ from one individual to the next. These host or germline differences have been shown to account for disease susceptibility, response to therapy, predisposition to side effects and thus may account for differences in outcome between patients with the same diagnosis. Advances in high throughput genetic techniques have made it possible to scan genomes for differences that might be associated with incidence and outcome.

Familial cases of ALL are quite rare but germline *TP53* mutations, characteristic of the Li-Fraumeni syndrome, are associated with ALL and 50% of patients with low hypodiploid ALL carry germline *TP53* mutations (29). Thus such cases should be screened since a finding of a germline *TP53* mutation is significant for genetic counseling of family members. Likewise mutations in the B cell transcription factors *PAX5* and *ETV6* have been seen in other rare cases of familial ALL (30, 31).

Many groups of investigators have done GWASs on children with ALL comparing the SNPs with unaffected controls. For the most part these studies have included children from North American and Europe. Variants in *ARID5B*, *IKZF1*, *CEBPE*, *CDKN2A*, *PIP4K2A* and *GATA3* have repeatedly been linked to a higher risk of developing ALL (32–35). The mechanistic explanation that links these genes to cancer predisposition is uncertain since many of them occur in non-coding introns. In some cases these variants were enriched in subtypes of ALL (e.g. *ARID5B* in hyperdiploid ALL and *GATA3* variants in Ph-like ALL) and the association of certain variants with ancestry explains the higher incidence of ALL in Hispanics compared to Europeans and Africans (35).

SNPs have also been associated with treatment outcome and adverse effects of treatment such as myelosuppression (many agents), pancreatitis (asparaginase related), osteonecrosis (glucocorticoids) and neuropathy (vincristine) (reviewed in (35)). Purine analogues such as 6-MP and 6-TG are cornerstones of therapy and the active products are metabolized by the enzyme thiopurine methyltransferase (TPMT). Patients with hypofunctioning variants (especially homozygous) show much greater levels of active metabolites and therefore a greater incidence of myelosuppression and therapy intolerance (36–38). Likewise a new study links a coding variant in *NUDT15* with thiopurine intolerance and such variants are more common in patients of East Asian and Hispanic ancestry (39). Some investigators recommend screening for TPMT variants so that dose can be adjusted before profound myelosuppression. In some (but not all) studies defective TPMT variants were associated with a more rapid response to treatment and a better outcome (40).

With the exception of TPMT and possibly NUDT15 the SNPS associated with response and adverse effects do not explain the vast majority of the events that occur in patients. Thus their routine integration into clinical decision making is not yet practical, but is a goal of emerging precision medicine approaches intended to maximize cure rates and avoid harmful side effects.

Optimizing CNS therapy to prevent neurocognitive toxicity

The burden of ALL therapy can be substantial with approximately 40% of childhood cancer survivors experiencing a serious late effect although fortunately data from more contemporary studies indicate that the burden may be significantly less (41). One of the most troubling late effects is cognitive impairment due to cranial irradiation (42, 43). While only 2% of children have overt leukemia in the spinal fluid at diagnosis the majority of children will suffer a CNS relapse if given systemic therapy alone. Indeed the use of presymptomatic craniospinal irradiation was one of the most important advances in the treatment of ALL (44). Radiation doses were subsequently decreased and therapy limited to the brain but many children were still left with neurocognitive impairment that manifested as impaired processing speed, global intellectual functions and executive function. A number of randomized studies have shown that intrathecal chemoprophylaxis with methotrexate (and sometimes “triple” therapy with cytarabine, hydrocortisone and methotrexate) can replace cranial irradiation with no impact on long-term outcome (45). Many of these studies intensified systemic therapy by substituting dexamethasone for prednisone (better CNS penetration), higher dose methotrexate and more frequent use of asparaginase reducing the CNS relapse rate to 6% or less (46). Only those patients with overt CNS disease at diagnosis and certain ALL subtypes with high risk for CNS failure are given cranial irradiation usually at lower doses (1200 to 1800 cGy).

Recently the complete abandonment of cranial irradiation has been incorporated into frontline trials even for patients with overt CNS disease at diagnosis (47, 48). Pui showed that by augmenting systemic therapy, using triple IT therapy, reducing traumatic lumbar punctures (associated with contamination of the CNS with peripheral blood blasts), and using risk stratified therapy that included minimal residual disease testing achieved a superior 5 year EFS (93.5%) with only 2.7% of patients suffering a CNS relapse (47). Moreover salvage for such patients who relapse without prior cranial irradiation is much better than those who receive cranial irradiation.

Conclusions

Treatment of childhood ALL is one of the major successes of modern medicine and has provided a paradigm for how cancer survival can be steadily increased through cooperative group clinical trials. New genomic discoveries and precision medicine approaches have the potential to both increase survival, and decrease short- and long-term adverse events. The biggest challenge is exporting improvements in care to low and middle income countries worldwide. In many middle income countries ALL survival rates are about 50%, similar to those of the late 1970s in high income countries (49). In low income countries, few children

with ALL survive leading to loss of millions of productive years of life. Our goal must be to cure all children who develop ALL, wherever they reside.

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Key Points

- Newly discovered genetic alterations that drive high risk Ph-like ALL can now be targeted with TKIs and JAK inhibitors leading to clinical trials for this particularly high risk subset.
- Novel immunotherapeutic approaches using BiTE antibodies and CAR T cells offer great promise in treating relapse ALL a leading cause of cancer cell death in children.
- The discovery of relapse-specific mutations provides an explanation for clonal evolution, drug resistance and the possibility of designing therapy to prevent relapse.
- Host genetic polymorphisms are associated with predisposition to childhood ALL, response to therapy and side effects.
- CNS irradiation can be limited to a very small subset of patients at initial diagnosis or abandoned completely thereby reducing neuropsychological sequelae of therapy.

Figure 1. Immunotherapy for ALL

A. An engineered CAR T cell engaging a leukemia cell through interaction of the T cell's single chain anti CD19 extracellular domain with the leukemia cell's surface CD 19. The T cell is activated through the intracellular domains of two co-stimulatory molecules and the CD3 zeta domain. B. a single chain BiTE polypeptide links with specificity for T cells (CD3) and leukemia cells (CD19) resulting in an immunological synapse. Figure based on references (10, 15)

Figure 2. Clonal Evolution of Relapse

Top to bottom. In many cases the leukemia at relapse emerges from a small clone at diagnosis. Leukemia cells at diagnosis may acquire additional genetic defects that result in therapy resistance. About half of all relapses appear to result from expansion of an ancestral clone. Rarely relapses are the result of a secondary cancer unrelated to the initial diagnosis and possibly caused by the mutagenic effects of therapy. Figure based on references (20, 21)