RECENT ADVANCES IN ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN AND ADOLESCENTS: AN EXPERT PANEL DISCUSSION

Barbara L. Asselin, Paul Gaynon, and James A. Whitlock
Recent Advances in Acute Lymphoblastic Leukemia: Pediatric and Adolescent Patients
An Expert Panel Discussion

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Recent advances in acute lymphoblastic leukemia in children and adolescents: an expert panel discussion

Barbara L. Asselin, Paul Gaynon, and James A. Whitlock

Purpose of review
Acute lymphoblastic leukemia (ALL) is the most common form of childhood leukemia, representing 75% to 80% of cases of acute leukemia among children. Dramatic improvements in the cure rates and survival outcomes for children with ALL have been seen over the past several decades; currently the 5-year survival rate for childhood ALL is more than 80%. These improvements have come about because of advances in the understanding of the molecular genetics and pathogenesis of the disease, incorporation of risk-adapted therapy, and the advent of new targeted agents.

Recent findings
Scientific advances have provided new insights into leukemogenesis, drug resistance, and host pharmacogenomics, identified novel subtypes of leukemia, and suggested potential targets for therapy. At the same time novel monoclonal antibodies, small molecule inhibitors, chemotherapeutics, and cell-based treatment strategies have been developed and investigated.

Summary
In this article, experts will discuss some of the current challenges and future directions in the treatment of pediatric ALL. The authors will offer expert guidance to practicing oncologists on how to best incorporate newer treatment approaches into the care of children and adolescents with ALL. The most important ongoing clinical trials in the area will also be reviewed.

Keywords
acute lymphoblastic leukemia, adherence, emerging agents, relapse, risk stratification

Learning objectives: After participating in this activity, physicians should be able to outline current challenges in the frontline treatment of children and adolescents with acute lymphoblastic leukemia (ALL); describe differences in risk stratification and treatment approaches for ALL in adolescents as compared with younger children; discuss important ongoing clinical trials in ALL and their potential impact on the management of ALL in children and adolescents; list promising emerging approaches to the treatment of ALL in children and adolescents; and identify potential treatment options for children and adolescents who relapse despite current therapy for ALL.

Editor's note: ALL is the most common form of childhood leukemia, representing about 85% of cases of acute leukemia among children [1]. Over the last several decades, advances in the treatment and supportive care of pediatric ALL have dramatically increased its 5-year survival rates to about 90% [2]. Risk-adapted treatment allocation may optimize outcomes and spare many patients from unnecessarily aggressive regimens. Despite these improvements, however, a considerable number of children with ALL still relapse and most who relapse die. Recently, a group of experts in the treatment of children and adolescents with ALL came together to discuss current challenges facing pediatric oncologists, including recent advances in...
risk stratification and the most promising areas of current ongoing research.

CURRENT CHALLENGES IN THE FRONTLINE TREATMENT OF CHILDREN AND ADOLESCENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Relapse

Dr Gaynon: Despite our good and improving therapy, perhaps one patient in 10 still suffers relapse [3–5]. Because ALL is so common, one relapse in 10 means that more children have ALL and relapse than have newly diagnosed acute myeloid leukemia (AML). Over the past 20 years, survival after diagnosis has improved for every subset of children except infants [3]. However, survival after relapse remains unchanged over the same interval, despite intensive chemotherapy, improving supportive care, and widespread use of hematopoietic stem cell transplant [6].

Many have asserted that contemporary patients, relapsing despite superior current treatments, are more difficult to treat than past patients, who relapsed after inferior past treatments. Freyer et al. [7] re-analyzed data from CCG 1961, a randomized trial evaluating intensified therapy for National Cancer Institute (NCI) high-risk ALL patients. They found that patients who relapsed on the inferior standard-strength regimens had no better outcome than patients who relapsed on the superior augmented regimens. Whereas some patients may be cured after extramedullary or late marrow relapse, few are cured after early marrow relapse, that is, relapse within 3 years of diagnosis.

Late effects

Dr Asselin: One of the things that we are now faced with is actually the problem of our success; that we have in fact made noteworthy strides in treatment of ALL for a considerable number of our pediatric patients, but those children are at risk for significant toxicity, especially late effects of those treatments. The estimate of 5-year survival from Surveillance, Epidemiology and End Results data collected on children treated from 2000 to 2004 was 87.5% [8]. In 2012, Hunger et al. [3] reported the Children’s Oncology Group (COG) experience from 1990 to 2004, noting an improvement in overall survival for children with ALL enrolled on a COG trial from 83.7 to 90.4% (Fig. 1). Further analysis of these clinical trials showed that this improvement was attributable to a decrease in the risk for relapse. The Childhood Cancer Survivor Study, a multiinstitutional cohort study of over 10000 adult survivors who were diagnosed with childhood cancer between 1970 and 1986, found a statistically increased frequency of chronic illness compared with siblings (Table 1) [9]. The cumulative incidence of chronic health conditions increased steadily over 20 years of follow-up across cancer subgroups, including leukemia [9].

We now have a group of children who are likely cured, but our focus has shifted to their future quality of life, and we need to support them through survivorship – being able to get back to normal life, get back to school, and back to being kids. The most common late effects including avascular necrosis (AVN), altered cardiac dysfunction, cognitive dysfunction, delayed growth, infertility, and second malignant neoplasm are associated with significant burdens with far reaching effects on mobility, school performance, employment opportunities, pain, independence, physical, social and emotional well being [10,11]. The challenge is to design treatment protocols that produce fewer disabilities without compromising antileukemic efficacy, and thus strike a balance between cure and long-term toxicity.

Dr Whitlock: In the past, we focused so much on survival and now we focus on not only survival but also quality of life. What does it mean to cure a patient of leukemia if they are a cardiac cripple because of anthracycline toxicity, or are infertile because of cyclophosphamide or immobilized because they have multiple bone and joint complications from AVN of bone caused by steroids? It is not enough to have more cures; we need to also be focusing on having better cures.

And that means that we are going to have to get rid of some of the drugs that we have had in our
Armamentarium for many, many years because the price that these children pay for cure is just too high – we need to not only have a higher cure rate but a better quality of cure.

Barbara and Paul, you often remind us that we may need to rethink what we use to measure treatment success and that our old way of basing that on 5-year event-free survival (EFS) is incomplete.

Dr Gaynon: The 5-year EFS does not reflect the quality of survival. I have patients alive and in remission with total hip replacements for AVN. In a young person, hips wear out about every 10 years. I have a patient alive and in remission with terrible leukoencephalopathy. She speaks about 10 words and will never be able to live on her own. These patients count as cures in our EFS statistics. We need more comprehensive measures to assess the impact of our therapies.

Adherence

Dr Whitlock: Another issue we have learned recently with adolescents is adherence; you have to take your oral medications for them to be effective. There have been important advances in documenting what many of us suspected, which is that some adolescents are not compliant with their oral medications [12]. This is now recognized as a significant reason that adolescents may fare more poorly and that becomes a real management challenge.

Risk stratification

Two strategies have brought us to where we are today, namely, risk-based treatment allocation and postinduction intensification.

Dr Asselin: We are also now coming to recognize that there are subsets of patients who we may not be able to identify at the outset, but for whom our treatment will be inadequate and we will not be able to control their disease. Childhood ALL is a heterogeneous disease with numerous subsets that can now be defined by clinical features (age, white blood cell count, sex, and race), immune phenotype (B-lineage, T-lineage, ambiguous), cytogenetic abnormalities (aneuploidy, trisomies, recurring translocations: tel-AML1, ETV6/RUNX1), gene rearrangements [mixed lineage leukemia (MLL)], and alterations in gene expression (IKAROS, JAK, CRLF2). With relapse of disease still the primary barrier to successful treatment, the traditional risk stratification according to NCI criteria of age and initial white blood cell count is not sufficient to identify patients at high risk for relapse. Although the majority of patients who will relapse have high-risk disease apparent at time of diagnosis, there is a significant minority of standard risk patients who relapse and ultimately die from disease progression or treatment complications [3].

We are faced with the challenge of trying to find better ways to identify those patients earlier and then bring the best therapies to the table so that they are available for children and more quickly than traditionally.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Survivors (N = 10,397) [percent]</th>
<th>Siblings (N = 3,034) [percent]</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major joint replacement(^a)</td>
<td>1.61</td>
<td>0.03</td>
<td>54.0 [7.6–386.3]</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.24</td>
<td>0.10</td>
<td>15.1 [4.8–47.9]</td>
</tr>
<tr>
<td>Second malignant neoplasm(^b)</td>
<td>2.38</td>
<td>0.33</td>
<td>14.8 [7.2–30.4]</td>
</tr>
<tr>
<td>Cognitive dysfunction, severe</td>
<td>0.65</td>
<td>0.10</td>
<td>10.5 [2.6–43.0]</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.11</td>
<td>0.20</td>
<td>10.4 [4.1–25.9]</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1.56</td>
<td>0.20</td>
<td>9.3 [4.1–21.2]</td>
</tr>
<tr>
<td>Renal failure or dialysis</td>
<td>0.52</td>
<td>0.07</td>
<td>8.9 [2.2–36.6]</td>
</tr>
<tr>
<td>Hearing loss not corrected by aid</td>
<td>1.96</td>
<td>0.36</td>
<td>6.3 [3.3–11.8]</td>
</tr>
<tr>
<td>Legally blind or loss of an eye</td>
<td>2.92</td>
<td>0.69</td>
<td>5.8 [3.5–9.5]</td>
</tr>
<tr>
<td>Ovarian failure(^c)</td>
<td>2.79</td>
<td>0.99</td>
<td>3.5 [2.7–5.2]</td>
</tr>
</tbody>
</table>

CI, confidence interval. Reprinted with permission from [9].
\(^a\)For survivors, major joint replacement was not included if it was part of cancer therapy.
\(^b\)For both groups, this category excludes basal-cell and squamous-cell carcinoma (grade 2). For siblings, this category includes a first cancer.
\(^c\)Values are for women only.
overtreating some patients. Some of our patients do not need continued intensification of therapy, and we need to spare those patients who can be cured with less therapy from all of the unnecessary toxicities.

For many years, we have relied on clinical features of the disease to help us prognosticate and subsequently to tailor therapies so we have been able to look at things like a child’s age, and initial white blood cell count. Subsequently, we have been able to look at early response in ALL, initially through studies in which Paul was very much involved. The International BFM Study Group has shown that early response of peripheral leukemic blasts to prednisone is a strong predictor of outcome; subsequently, the Children’s Cancer Group (CCG) showed that early response as measured by persistent blasts in the bone marrow after an initial 1–2 weeks of treatment is also a strong predictor of outcome [13].

The use of morphologic evaluation of a reduction in blasts has been greatly refined in the last few years with more precise methodologies, such as flow cytometry (the predominant method in North America) and the PCR, to more accurately quantify minimal residual disease (MRD) after initial treatment. MRD has been shown in multiple studies conducted by multiple cooperative groups using various methodologies to be one of the best, if not the best, predictor of subsequent outcome after initial therapy [14,15].

And it is fair to say that probably all of us regard MRD testing now as a standard of care, that it is integrated into all of the current contemporary treatment protocols and that we increasingly rely on the use of MRD to make decisions about which patients can have their therapy reduced, and which patients need to have their therapy further intensified in some way. MRD is one test that is now rapidly entering practice in a broad way and is used not only for patients who are treated on cooperative group protocols, but increasingly for patients who are not enrolled on clinical trials. How rapidly a patient’s leukemia clears is a strong predictor of how that patient will respond to subsequent therapy and that has been greatly refined in the last few years with MRD testing.

Dr Asselin: Taking a step back, the recognition of this biologic heterogeneity, the diagnostic testing that is part of making the diagnosis of ALL has become more and more sophisticated. It no longer involves simply looking through the microscope at blood or bone marrow. Specific genetic abnormalities, such as double trisomy 4 + 10 or RUNX1/ETV6, can be identified in almost 100% of children if they are very carefully evaluated and the leukemia cells are tested (Fig. 2, Table 2) [4,16–33].

And so what we used to call ALL is not just ALL anymore. Within that diagnosis, there are significant differences that are important to establishing the correct diagnosis that hopefully someday will

**FIGURE 2.** Estimated frequency of specific genotypes in childhood leukemias. Genetic abnormalities in acute lymphoblastic leukemia. Reprinted with permission from [4].
### Table 2. Characteristics and clinical outcomes of selected subtypes of childhood acute lymphoblastic leukemia

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Frequency (%)</th>
<th>Clinical implication</th>
<th>Estimated 5-year event-free survival (%)</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell precursor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperdiploidy (&gt;50)</td>
<td>20–30</td>
<td>Excellent prognosis with antimetabolite-based therapy</td>
<td>85–95</td>
<td>Pui et al. [16,17]</td>
</tr>
<tr>
<td>t(12;21)(p13;q22) ETV6-RUNX1</td>
<td>15–25</td>
<td>Expression of myeloid-associated antigens CD13 and CD33; excellent prognosis with intensive asparaginase therapy</td>
<td>80–95</td>
<td>Pui et al. [16,17]</td>
</tr>
<tr>
<td>Trisomies 4 and 10</td>
<td>20–25</td>
<td>Excellent prognosis with antimetabolite therapy</td>
<td>85–90</td>
<td>Saller et al. [18]</td>
</tr>
<tr>
<td>t(1;19)(q23;p13) TCF3-PBX1</td>
<td>2–6</td>
<td>Increased incidence in blacks; excellent prognosis with high-dose methotrexate treatment; increased risk of CNS relapse in some studies</td>
<td>80–85</td>
<td>Pui et al. [16,17]</td>
</tr>
<tr>
<td>Intrachromosomal amplification of chromosome 21</td>
<td>2–3</td>
<td>More common in older children and adolescents; poor prognosis; benefit from intensive induction and early re-intensification therapy</td>
<td>30–40</td>
<td>Attarbaschi et al. [19]</td>
</tr>
<tr>
<td>t(4;11)(q21;q23) MLL-AF4</td>
<td>1–2</td>
<td>Poor prognosis and predominance in infancy, especially those &lt;6 months of age; overexpression of FLT3</td>
<td>30–40</td>
<td>Pui et al. [16,17]</td>
</tr>
<tr>
<td>t(9;22)(q34;q11.2) BCR-ABL1</td>
<td>2–4</td>
<td>Imatinib and intensive chemotherapy improve early treatment outcome</td>
<td>80–90 at 3 years</td>
<td>Schultz et al. [20]</td>
</tr>
<tr>
<td>t(1;19)(q23;q32.3)</td>
<td>2</td>
<td>Favorable prognosis with short-term intensive therapy with high-dose methotrexate, cytarabine, and cyclophosphamide</td>
<td>75–85</td>
<td>Pui and Evans [21]</td>
</tr>
<tr>
<td>Hypodiploidy (&lt;44 chromosomes)</td>
<td>1–2</td>
<td>Poor prognosis</td>
<td>35–40</td>
<td>Nachman et al. [22]</td>
</tr>
<tr>
<td>CRLF2 overexpression (55%)</td>
<td>6–7</td>
<td>Poor prognosis; common in patients with Down syndrome</td>
<td></td>
<td>Mullighan et al. [23], Cario et al. [24], Harvey et al. [25]</td>
</tr>
<tr>
<td>T-cell</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>TAL/IMO rearrangement</td>
<td>15–30</td>
<td>Good prognosis in some studies; potentially responsive to histone deacetylase inhibitor</td>
<td></td>
<td>Meijerink et al. [26]</td>
</tr>
<tr>
<td>HOX11 rearrangement</td>
<td>7–8</td>
<td>Good prognosis</td>
<td></td>
<td>Meijerink et al. [26]</td>
</tr>
<tr>
<td>HOX11L2 (TLX3) rearrangement</td>
<td>20–24</td>
<td>Poor prognosis in some studies</td>
<td></td>
<td>Meijerink et al. [26]</td>
</tr>
<tr>
<td>HOXA rearrangement</td>
<td>4–5</td>
<td>Poor prognosis; potentially sensitive to histone H3K79 methyltransferases inhibitor</td>
<td></td>
<td>Meijerink et al. [26]</td>
</tr>
<tr>
<td>NUP214-ABL1</td>
<td>6</td>
<td>Sensitive to tyrosine kinase inhibitor</td>
<td>&lt;50 (survival)</td>
<td>Graux et al. [27]</td>
</tr>
<tr>
<td>MLL-ENL</td>
<td>2–3</td>
<td>Favorable prognosis</td>
<td>80–90</td>
<td>Pui et al. [16]</td>
</tr>
<tr>
<td>Early T-cell precursor</td>
<td>12</td>
<td>Poor prognosis; expressed myeloid or stem-cell markers</td>
<td>30–35</td>
<td>Coustan-Smith et al. [28]</td>
</tr>
<tr>
<td>Cooperation mutations</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>B-cell precursor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IKZF1 deletions/mutations</td>
<td>15–30</td>
<td>Poor prognosis; resistant to asparaginase and daunorubicin</td>
<td>50–55</td>
<td>Den Boer et al. [30]</td>
</tr>
<tr>
<td>JAK mutations</td>
<td>92–5</td>
<td>Predominance in high-risk patients; JAK2 mutations in 20% of Down syndrome cases; potentially responsive to JAK2 inhibitors</td>
<td>~60</td>
<td>Mullighan et al. [31]</td>
</tr>
<tr>
<td>T-cell</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOTCH/FBXW7 mutations</td>
<td>50</td>
<td>Favorable prognosis; potentially responsive to NOTCH inhibitor</td>
<td>90</td>
<td>Breit et al. [32]</td>
</tr>
<tr>
<td>P13K-AKT pathway</td>
<td>~50</td>
<td>Poor prognosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDKN2A/2B deletions</td>
<td>~70</td>
<td>Poorentially responsive to DNA methyltransferases inhibitor</td>
<td></td>
<td>Meijerink et al. [26]</td>
</tr>
</tbody>
</table>

Reprinted with permission from [4].
help identify the better treatments for a particular patient.

It has been interesting to see MRD finally make it to the frontline, after so many years of hearing about it and to see it now take its place as a validated early measure of response to treatment, an important biologic feature in risk stratification and modification of treatment intensity at an early phase.

Dr Gaynon: I think we are coming to the end of our general intensification of therapy. As our cure rate increases, the ‘number needed to treat’ increases exponentially. In order to win one more cure, we have to subject more and more children to more and more aggressive therapy. With a 40% cure rate, we fought our way to 60%. We had to treat five children to gain one more cure. With an 85% cure, we may fight our way to 90%, but we have to treat 20 children to benefit one.

Early identification of those patients for whom current therapy is inadequate is crucial. We began with age and white blood cell count, then added immunophenotype and cytogenetics. Cytogenetics enables us to identify higher risk subsets like Philadelphia chromosome (Ph)-positive ALL, severe hypodiploidy, MLL rearrangements, and internal amplification of chromosome 21. MRD, quantification of residual leukemia in a microscopically remission bone marrow, has proved a robust prognostic factor.

In the current COG scheme, infants and young people with Ph-positive ALL are assigned to special protocols. All patients older than 13 years are assigned to a very high-risk stratum with patients with central nervous system (CNS) leukemia at diagnosis, severe hypodiploidy, internal amplification of chromosome 21, or MLL gene rearrangement, standard risk patients lacking favorable cytogenetics with high end induction MRD, or higher-risk patients with high end induction MRD. Among patients older than 16 years, treatment deaths account for a higher percentage of treatment failures, though benefit was seen for intensive schemes of postinduction intensification.

**IMPORTANT ONGOING CLINICAL TRIALS**

Dr Gaynon: Today’s therapy is the end result of 50 years of clinical trials. We are still moving forward. We have learned to use conventional agents better. Recent COG trials showed a benefit for dexamethasone and intravenous (i.v.) escalating-dose methotrexate in standard risk patients and for high-dose methotrexate in higher risk patients. Dexamethasone was also found useful for younger higher risk patients. Eric Larsen earned a plenary session presentation at the 2011 American Society of Clinical Oncology meeting. A few years before Kirk Schultz shared COG data at an ASH plenary session, reporting markedly better outcomes in Ph-positive ALL, when a tyrosine kinase analogue was added to intensive chemotherapy.

Current COG trials are evaluating clofarabine in very high-risk B-precursor ALL and nelarabine in T-cell ALL. The Medical Research Conference (UK) is seeking whether the continuous steroids in induction can be safely replaced with an intermittent schedule, 7 days on, 7 days off, and 7 days on to decrease the incidence of osteonecrosis of bone. St Jude Children’s Research Hospital continues its good work and explores the value of hematopoietic stem cell transplant in patients with persistent MRD. Just as past trials have defined the current standard of care, any of these ongoing trials may change the standard of care further.

Dr Whitlock: This discussion is reflective of one of the trends that we are going to see increasing in clinical trials for childhood ALL, which is that international collaboration is becoming more common really out of necessity.

We have talked about how ALL is not one disease or two diseases but really at the molecular level, 15, 20, or 30 or more diseases. As we begin to develop therapies that target one subgroup that may not be effective against the others, we have rapidly diminishing numbers of patients to include in our clinical trials. Therefore, one of the trends that we are certainly going to see emerging over the coming years is the need for international collaboration. The first example of that is an international trial for children with Ph-positive ALL that is evaluating a second-generation tyrosine kinase inhibitor, dasatinib (NCT01460160). This study is a collaborative effort between the COG and the European Intergroup Study on Post Induction Treatment of Philadelphia Positive Acute Lymphoblastic Leukaemia with Imatinib (EsPhALL).

I think it is very likely that the next study that we do in infants will also be an international collaboration between two or three very large groups because that is the only way we can really get the numbers that are going to be necessary for such a trial.

Dr Asselin: The ongoing trials within the COG with successful completion should help us answer some important questions both about certain subgroups of children with ALL and their treatment, such as the use of clofarabine in very high-risk B-precursor ALL (AALL131) and nelarabine in T-ALL (AALL0434) [34]. And some of these trials for newer drugs, for example, the phase II trial of bortezomib (AALL07P1) and blinotumomab will show us the potential response and effectiveness
of ALL to immunotherapy. We may get a better sense of how to use immunotherapeutic agents from those trials. In addition, ongoing trials are designed to answer questions about supportive care (e.g., use of prophylactic antiinfectives, burden of care, late effects, and quality of life). Some of the international collaborative trials are in process, like those evaluating dasatinib and Interfant, and some have not yet started. I too want to emphasize the importance of these large international cooperative trials to get adequate patient numbers to really be able to learn something and especially spark discussions related to infants and future collaborations.

Dr Gaynon: That is a very good point. We rarely mention infants because that is the one subset in which we have not been able to show a significant improvement in outcome in the past 20 years [3]. The international trials mentioned above may give us a chance to do something more useful for infants, but we need to have a compelling research question to encourage everybody to put aside their proprietary regimens and collaborate.

Dr Asselin: You are right, because right now our definition of risk is based on risk for relapse, which is only one feature that may be shared among that group of patients and does not necessarily distinguish the different biologic subtypes.

Dr Gaynon: Barbara Asselin’s POG 9404 study [35] added i.v. methotrexate to the Dana Farber Cancer Institute treatment platform for T-cell (T)-ALL and T-lymphoblastic lymphoma. Intravenous methotrexate improved outcome in the T-ALL subset substantially, numerically diminished outcome in the T-lymphoblastic lymphoma subset, and had no statistically compelling effect in the aggregate analysis.

With biologically heterogeneous populations, we are taking a risk that an intervention will have a heterogeneous effect – helpful for some patients and detrimental for others. In the future, we are likely to group patients according to their biology, including patients with different outcomes, but sharing a similar biology, for example, acute promyelocytic leukemia (APL) and Ph-positive ALL. I am hoping that our friends Jim Downing, Charles Mullighan, Bill Carroll, and Cheryl Wilman will help us learn more about these biological subsets.

Dr Whitlock: So Paul, maybe what you are saying is that in the era in which we only had a very limited number of treatment approaches for leukemia, we had a hammer and everything looked like a nail.

Dr Gaynon: And boy, we got lucky for a while!

Dr Whitlock: Yes, and it has worked, but it is not very refined, and now we are entering an era in which we have lots of different types of hammers and suddenly maybe all the nails are not exactly the same.

Dr Whitlock: One of the most dramatic advances in the past 5–10 years has been the early use of imatinib in children with ALL with the Ph-positive ALL. The addition of imatinib to intensive chemotherapy more than doubled the 3-year event-free survival of these patients in a COG study [20]. This is really the proof-of-principle that targeted therapy – the right drug in the right dose against the right target – can have a dramatic impact on high-risk leukemia. Historically, Ph-positive ALL has been among the worst actors that we deal with in childhood ALL, even with stem cell transplantation. And now with a drug that is oral and relatively nontoxic, we have seen that outcomes can be dramatically improved to the point that in the current COG/ESPhALL study, we are beginning to test the concept of whether some children with Ph-positive ALL can avoid stem cell transplants. This would have been unthinkable 15–20 years ago so to me that is probably the most dramatic advance in the last decade in the terms of childhood ALL.

EMERGING APPROACHES TO THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN AND ADOLESCENTS

Minimal residual disease testing

Dr Gaynon: Emerging data suggest that persistence of MRD or reappearance of MRD may identify patients destined to relapse despite our generally effective therapy. MRD has proven a robust prognostic factor in newly diagnosed and relapsed ALL. Currently, we incorporate end induction MRD in treatment allocation. Emerging data suggest that patients with persistent MRD, 3 months from diagnosis have about a 50% chance of relapse. Gokbuget et al. [36] from the German Multicenter Study Group for Adult ALL find strong data in adults to support this notion and a strong hint that early intervention, including hematopoietic stem cell transplant may alter the dire prognosis.

Based somewhat on the experience in APL [37] and the reports from Germany [36], is there a window which you can identify failure before the leukemia collects the evil clones that ultimately cause the patient’s demise? We have limited data using flow cytometry for the later endpoints. I would say there are much more data with PCR. First, we have to identify disease reliably and then we can see what we can do about it.
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If we falsely identify a patient as being destined to failure and then do whatever we do and the patient does well, and then we will say, look how clever we are! There is always a risk of a ‘false positive’ treatment failure. Because most patients are cured, the chance for false positives is increased. Biology may play a nonrandom role. In patients with AML and t(8;21), the translocation may persist for some time, even though the patient is cured.

New agents

Dr Asselin: Drug development takes an incredibly long time. Because of additional safety testing required in children, our kids and young people get access last and often cannot get access. Between 1948 and 2003, the US Food and Drug Administration (FDA) approved 120 anticancer drugs, 15 have a specific pediatric indication [38]. Drug development is expensive and the pediatric market rarely justifies the $800 million cost to move a drug from the laboratory to the clinic. A serious adverse event in a child may ‘go viral’ and taint a candidate agent. In 2004, clofarabine was approved for a pediatric indication without prior approval for an adult indication, a rare event [38]. It is more common for children to get ‘hand me down’ drugs designed for adult indications that are eventually and reluctantly studied in pediatric cancer.

An agent that only has an indication in children, that is not efficacious for anything in the larger adult market, will often not be developed any further and so we have run into that brick wall on occasion which can be very frustrating. In a 2012 editorial, Norris and Adamson [39] review the historical barriers to pediatric cancer drug development. They emphasize that high priority targets for drug development in adult cancers should not be merely extrapolated to pediatric cancer treatment. With the advent of new molecularly targeted anticancer therapy, they point out that collaboration among the biopharmaceutical industry, governmental agencies, academic medical institutions, and clinical cooperative groups is paramount for continued progress in treatment of children with cancer. I think that drug development is a major challenge to be faced in the future.

Dr Gaynon: If this study had been terminated because they found no difference in MRD, they would never have seen the difference in the PFS that they found. In studies comparing prednisone and dexamethasone by both the British and German groups, there was no difference in MRD, but there was a PFS advantage for dexamethasone [41,42]. So although I was hoping that MRD could be a valid surrogate, MRD is not a surrogate and complete remission rate probably is not a complete surrogate either.

Dr Asselin: And molecular remission may not be even a sufficient definition.
Dr Gaynon: MRD is a wonderful prognostic factor, but, as discussed above, it is not as wonderful as a surrogate. We are increasingly aware that leukemia is oligoclonal and when we achieve a remission, we kill the predominant clone. The laboratory tells us that when the leukemia comes back, that predominant clone at relapse differs genetically from the predominant clone at presentation in detectable ways in more than 90% of cases [43]. As a patient relapses, oligoclonal evolution continues. We often wipe out the predominant clone after a relapse, but often there is a new subclone that causes the second relapse and so on.

Recently, our Therapeutic Advances in Childhood Leukemia (TACL) consortium reported promising data with bortezomib in combination with a standard four-drug reinduction. We have great hopes for the immunotoxins like inotuzumab and moxetumomab and immune constructs like blinatumomab. Preliminary results with chimeric antigen receptor modified T-cells have created quite a stir [44]. However, one might suggest that blasts become resistant to multiple classes of chemotherapeutic agents when they have defects in shared cell death pathways. Most agents work through apoptosis. If apoptosis is defective, prednisone will not work, nor will inotuzumab.

Unlike adult cancer in which they can treat, for example, a thousand people with breast cancer and see who responds, we cannot do that with childhood cancer, but at least we can have a hypothesis. Let the people who are developing a drug tell us what kind of patients they want. Most drugs fail for lack of efficacy and this way we can determine early whether or not the drug has any benefit in the population that seems most likely.

I always ask students to read Brian Druker’s Lasker prize essay [45] in which he recalls that in his development of imatinib he was told, ‘Why don’t you try this in all leukemias because it just might work? You might get lucky!’ He said that his hypothesis was that it could work in chronic-phase CML and if he did not get a response in chronic-phase CML, he was not really interested. We all know that the clinical need is urgent. We work hard and hope we are going to do something useful. We nurture a little fantasy that maybe this drug is going to be the one that is going to work. Most do not. The key is to identify the right drug for the right patient.

**POTENTIAL TREATMENT OPTIONS FOR RELAPSED ACUTE LYMPHOBlastic LEUKEMIA**

Dr Gaynon: We have made little progress in treating relapse in recent years [6].

Dr Whitlock: One of the challenges that we face in patients who relapse (at least in patients with high-risk or early relapse) is that a significant proportion will not even be able to attain another remission. In a COG study of first relapse patients (AALL01P2), only two-thirds of patients relapsing less than 36 months from diagnosis attained a second remission after a course of reinduction therapy. And among those who did attain a second remission, fully three-quarters of them had detectable MRD [46]. We do not face this challenge in patients with newly diagnosed ALL; virtually all of those patients will enter a remission, so this issue distinguishes relapse treatment from frontline therapy.

Another issue concerning relapse is that in an attempt to improve remission rates, we have tried many different very intensive regimens of cytotoxic drugs which are often at the limits of tolerability. In Paul’s CCG study for relapsed ALL, over 10% of patients died during reinduction therapy [47]. In our current protocols, we are seeing increasingly significant infectious complications, not just bacterial infections, but an increasing incidence of fungal infections that become huge challenges to manage.

The role of stem cell transplantation in ALL remains unclear. Dr Gaynon [47] conducted a randomized study a number of years ago that tried to answer this question in relapse, but did not show a clear advantage of allogeneic transplant over chemotherapy. Even today, we struggle with the role of stem cell transplantation in patients with relapse – which patients are likely to benefit from transplant, and in which patients is the standard approach to transplant likely to fail?

We know that stem cell transplantation has the potential to be curative. Most high-risk or early relapse patients will undergo allogeneic stem cell transplantation and yet many of those patients will relapse after transplantation and still die [48,49]. So whatever we are doing with transplantation, it is not as successful as it needs to be. Somehow we have to either find better therapies that will replace transplantation or we need to improve stem cell transplantation itself. MRD is proving to be an important tool for stratifying patients for transplant. A study in relapsed ALL patients from the BFM group found that patients with detectable MRD prior to allogeneic transplant had a significantly worse outcome than those without detectable MRD prior to transplant, indicating that MRD is an important prognostic factor for posttransplant outcome [50].

Dr Gaynon: I hope that we can someday replace stem cell transplant. Unfortunately, ablation is just one course of therapy and you only have a few days to deliver that therapy. Many of the agents
that Dr Whitlock is working on are promising. We talk about an immune effect and we have some interesting drugs like the bispecific T-cell engager (BiTE) construct blinatumomab [51].

Dr Whitlock: Yes, although I think it is fair to say that those are still so early in development that I do not think we really know what their impact is going to be. We are all very excited about it and we anticipate that they are going to be important contributors, but it is a little too early to declare success.

Dr Gaynon: I am getting more and more excited about our TACL study with the Toll-like receptor agonist that may enhance the immunogenicity of the leukemia cells [52]. Some interesting studies examine the role of the demethylating agents and immune modulation, by exposing the methylated CpG motifs for immune attack. Is there a subset of patients for whom epigenetic therapy makes more sense than for other subsets of patients; infants and older patients with MLL rearrangements, perhaps?

Dr Asselin: Yes, so certainly stem cell transplant is the example of us getting our biggest hammer and, you know, I am just not feeling that we have an alternative at this point so...

Dr Gaynon: And stem cell transplant has cured many children who are alive today, no question.

All too often I send a child to transplant and I feel like I am a success. The patient goes through transplant and then gets past the 100-day mark and the transplanter feels like he is a success too. Then the patient relapses 2 months later. The doctors are all successful, but the patient will get more toxic therapy, perhaps a second transplant, and then expire.

We really have no idea of the molecular changes that cause relapse. A recent paper about the defect in the gene that encodes for S'-nucleotidase reported promising findings. S'-nucleotidase is an enzyme that metabolizes 6MP [53]. Meyer et al. [53] found the mutation in a substantial subset of patients who have early relapse, but never in late relapse patients.

A group of patients may need a particular therapeutic approach that does not benefit other subsets. I expect we are going to learn something from this work that will help us direct appropriate patients to the most appropriate novel agents.

The key is to be able to understand the pathophysiology of treatment failure. We should be studying first, second, and third relapse samples to learn how leukemias evolve. Our so-called models are inadequate. Greaves’ work [54] on Darwinian evolution of a leukemia population explains so many things. When you grow leukemia cells in a Petri dish, the subclones that like Petri dishes grow. When leukemia cells grow in a patient, you may get different clones altogether.

Dr Gaynon: We are not there yet, but complete remissions have been achieved in clinical trials with blinatumomab [55]. When you see complete remissions in phase 1 studies, that is usually a very promising sign but again, if you kill the predominant clone, you have a remission. If you kill all the clones, you have a cure. I think there is a substantial difference between killing the predominant clone and killing all the clones.

**Differences in risk stratification and prognostic indicators in adolescents versus younger children**

Dr Gaynon: We see more Ph-positive leukemia in our older populations. When we have a 17-year-old with a 200000 white blood cell count and B-precursor leukemia, we want to make sure we are not dealing with Ph-positive leukemia. The important other factor in adolescents is that older teenagers are less tolerant of therapy. In the CSG-1961 study for patients over age 16, a quarter of adverse events were toxic deaths so that we have to be mindful of the specific challenge [56].

We see more asparaginase toxicity in the older patients and what I am seeing now, which I cannot recall in the past, I think I am seeing more chronic pancreatitis (personal observation). I have patients with one episode at the end of induction and then recurrent episodes of pancreatitis despite no further asparaginase during 2–3 years of therapy.

Dr Asselin: Well, yes, I have seen and also I hear about or get called about patients in that same situation and there are a couple of different things that it really brings to mind. Certainly, there are other drugs that are associated with pancreatitis. If you look at the medication list of these patients now, they often are on so many other supportive therapies with overlapping toxicities.

In older patients, we have to keep in mind the influence of alcohol or other drug use and then there are also genetic factors both in terms of general family history and some specific genotypes (e.g., cystic fibrosis gene abnormalities and genotypes) that genome-wide screening may help us to figure out. In the past, prognosis of ALL was related to disease control and the likelihood of cure of the leukemia.

But now it has also become important to take into account the different toxicity risks and all of the concerns about osteonecrosis and the fact that we have not put dexamethasone into induction regimens for the older patients for fear of AVN. This affects our treatment decisions both in terms of determining the best treatment to cure their
leukemia and finding the right balance of risk of late effects.

Dr Gaynon: Well, I thought it was very surprising that we have had dexamethasone and prednisone since the 1960s, but no one knew that adolescents metabolized these drugs more slowly than younger children so this illustrates how little we may know about the drugs that we use so frequently.

**THE CURRENT ROLE OF GENOME-WIDE ANALYSIS**

Dr Asselin: This is an area that is in its infancy because even though we can get information now, we do not know what to do with it. There was a time 20 years ago when we might have said the same thing about the study of MRD or tyrosine kinase inhibitors.

Dr Gaynon: Mary Relling and colleagues [57,58] wrote two papers on the 25 genes most associated with AVN. One paper used a St Jude cohort of patients and the other used the COG cohort of patients; of the 25 top genes in each group, there was not one gene that appeared on both lists [57,58].

There are seven or eight papers about which genes are turned on or off by steroids, and I think there is no gene mentioned in more than three papers [59], so this field is in its infancy and it is at high risk for false discovery.

Dr Whitlock: I think it is fair to say that genome-wide analysis has not yet entered our practice in a meaningful way. I think it is currently probably most effectively being used in discovering new therapeutic targets.

A project funded by the NCI, the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative, is looking for recurring genetic abnormalities in high-risk populations of patients including high-risk ALL and those studies are beginning to pay off in terms of identifying potential drug targets [60].

It is a little too early to say that that is a success; there have not been any real proof-of-principle trials yet. There have been some diseases in which there have been targets identified that have already been proven to be clinically relevant through the successful application of targeted therapies. I am not aware of any examples as of yet in ALL, but there is little doubt that that is going to happen. We just do not know when and so at the present time, I do not think any of us would recommend that for a patient who is not enrolled in a clinical trial, there is any reason to do genome-wide sequencing.

Dr Asselin: Data from the collaborative TARGET research program have identified Ikaros family zinc finger 1 (IZKF1), JAK kinases, and cytokine receptor-like factor 2 (CRLF2) as important to the biological mechanisms of some high-risk phenotypes of ALL [39].

**OTHER EMERGING APPROACHES**

Dr Whitlock: Some of the immunotoxins that are in development are very exciting drugs; in addition, there is this whole field of immunotherapy that has not played much of a role so far in the management of ALL other than in allogeneic stem cell transplantation.

And while, early on, many of us believed that the way stem cell transplantation worked was to kill the bad cells and then plant new seeds in the ‘soil’ of the recipient’s bone marrow. In fact, the primary benefit of allogeneic transplantation is now recognized to be through the graft versus leukemia (GVL) effect [61]. So as we better understand and learn how to manipulate and modulate that immunologic effect, we can ensure that all patients get some of that immunologic effect. If we could control it so well that no patient gets too much graft versus host disease (GVHD) and has a fatal or persistent complication of GVHD, we should be able to improve allogeneic stem cell transplantation in a significant way.

We have antibody-based therapies in development that are very promising in preclinical studies, and many of those are in or entering clinical trials, so we are going to see an increasing investigation of the role of various approaches of immunologic-based therapies in treating children with ALL.

Dr Asselin: We continue to hope that if we develop targeted therapies that we will find the best place to use them. The standard approach has always been to try new therapies in relapsed disease, and if the new therapy is successful, then move it into the frontline setting. I think some of what we know about genetics and host pharmacogenomics may really challenge that approach and may help us develop a better one so that some of these immunotherapies and other targeted therapies can be developed in the appropriate setting.

Dr Gaynon: I will come back and emphasize the possibility of early identification of treatment failure, that the data in APL I think are fairly convincing that patients who are diagnosed with return of the translocation 15;17 and have therapy initiated promptly do much better than patients who are not treated until overt clinical relapse occurs [36].

There is also the opportunity to try to identify relapse early, especially in T-cell ALL in which peripheral blood might be useful to look for evidence of MRD reappearing because in T-cell ALL you have got
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a very tight correlation between peripheral blood and marrow [62].

CONCLUSION

Dr Gaynor: I will quote Professor Giuseppe Masera who said that there was a time in his life when he wanted to chair every leukemia trial. Now, he just wants to live long enough to learn how they turn out. I have to second his wish. I hope we all live long enough to see how these things all turn out in the next 20 years or so.

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Conflicts of interest

REFERENCES


