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HOW I APPROACH

How we approach Philadelphia chromosome-positive acute lymphoblastic leukemia in children and young adults

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Abstract

Treatment for children with Philadelphia chromosome-positive acute lymphoblastic leukemia has changed radically over the past 20 years. This type of leukemia used to have dismal prognosis, but today cure rates have improved with combination of cytotoxic chemotherapy and a tyrosine kinase inhibitor such as imatinib or dasatinib, with hematopoietic stem cell transplant reserved for patients who are at high risk based on slow response to therapy or who relapse. Treating these patients can be challenging particularly if they are not enrolled on a clinical trial. Here, we describe our approach to these patients.

KEYWORDS
clinical trial, hematopoietic stem cell transplant, minimal residual disease, Philadelphia chromosome, tyrosine kinase inhibitor

1 | CASE 1

A 16-year-old male presented with a 3-week history of fevers, lymphadenopathy, and leg pain. On examination, he had petechiae and bruising. Platelets were 17 000 cells/μL, hemoglobin was 10.4 g/dL, white blood cell count (WBC) was 12.7 cells/μL, and absolute neutrophil count was 900 cells/μL with predominance of lymphocytes and some atypical lymphocytes. Flow cytometry of a marrow aspirate revealed 90% abnormal B-cell lymphoblasts expressing CD19, CD34, CD10, variable dim CD38, CD66c, variably dim CD45, without CD33, CD13, CD15, CD20, CD3, or CD117, consistent with B-cell acute lymphoblastic leukemia. His cerebrospinal fluid had no detectable leukemia cells. He started on four-drug induction therapy with prednisone, vincristine, daunorubicin, and pegaspargase. Seven days later, results revealed a karyotype 46,XY,t(9:22)(q34.1;q11.2)[18] and fluorescence in situ hybridization (FISH) showing *BCR-ABL1* fusion in 70% of cells.

Abbreviations: CI, cumulative incidence; CML, chronic myelogenous leukemia; CNS, central nervous system; COG, Children's Oncology Group; CR, complete remission; EFS, event-free survival; EsPhALL, European Ph$^+$ ALL study group; FISH, fluorescence in situ hybridization; HSCT, hematopoietic stem cell transplant; MRD, minimal residual disease; Ph$^+$, Philadelphia chromosome-positive; qRT-PCR, quantitative reverse transcriptase PCR; TKI, tyrosine kinase inhibitor

2 | INTRODUCTION

In the year 2000, cure rates for pediatric ALL in children had improved to greater than 85%.[1-5] However, outcomes for Philadelphia chromosome-positive (Ph$^+$) ALL remained dismal. An international retrospective study of 326 children with Ph$^+$ ALL treated between 1985 and 1996 showed that only 82% attained complete remission (CR), the 5-year event-free survival (EFS) rate was 28%, and overall survival (OS) was 40.[6] Hematopoietic stem cell transplantation (HSCT) in first remission (CR1) with a related donor was the best chance of cure in the pre-tyrosine kinase inhibitor (TKI) era,[6,7] but was only available for a subset of patients. HSCT was associated with a risk of early death and significant long-term toxicity. Furthermore, in the pre-TKI era, the 5-year disease-free survival (DFS) and OS for children with Ph$^+$ ALL transplanted in CR1 were only 44 and 54%, respectively.[7] The subsequent combination of intensive chemotherapy

with a TKI such as imatinib or dasatinib[8,9] has revolutionized the care of children, adolescents, and young adults with Ph+ ALL.

2.1 | Lessons learned from clinical trials

In contrast to chronic myelogenous leukemia (CML), where monotherapy with imatinib achieved durable complete remissions, the single agent effect of imatinib in patients with Ph+ ALL was transient.[10] Studies in adults showed that combining imatinib with multiagent chemotherapy was safe.[11-13] Based on these results, two large cooperative groups, the European Ph+ ALL study group (EsPhALL) in Europe[14] and the North American-based Children's Oncology Group (COG), conducted trials combining imatinib with chemotherapy in pediatric Ph+ ALL patients.[15] The randomized EsPhALL2004 trial demonstrated that imatinib (300 mg/m^2/day) plus chemotherapy was more effective than chemotherapy alone in good risk Ph+ ALL patients defined based on rapid response to prednisone and CR at the end of induction.[14] However, 80% of patients on the EsPhALL study, including 76.7% of good risk patients, underwent HSCT in CR1. In contrast, on the nonrandomized COG AALL0031 trial, imatinib (340 mg/m^2/day) was added to an intensive chemotherapy backbone initially in a phase 1 stepwise fashion until the feasibility and safety of using it throughout the 2-year treatment was established.[15] In AALL0031, only patients with matched-sibling donors (13/44 or 30%) were assigned to proceed to HSCT. This study resulted in a 70% 7-year EFS in patients receiving chemotherapy plus continuous imatinib postinduction.[16] While the number of patients enrolled was small, those receiving matched-sibling HSCT on study or alternative-donor HSCT off-study had similar outcomes to patients who received chemotherapy plus imatinib. These results changed the standard of care in pediatric Ph+ ALL. Today, only patients classified as high-risk patients based on minimal residual disease (MRD) are recommended to undergo HSCT in CR1.[17] The definition of who is high risk evolves over time, and a smaller percentage of patients have gone to transplant with each successor trial without significant drop in treatment efficacy.

On the AALL0031 trial, all patients received central nervous system (CNS) radiation to prevent recurrence. This intervention was based on trials in high-risk pediatric ALL patients conducted in the late 1990s that showed unacceptably high CNS relapse rates.[18] Subsequent COG and joint COG/EsPhALL trials moved away from routinely using radiation therapy to prevent CNS recurrence, and reserve it for patients with overt CNS disease at diagnosis.

The successor COG AALL0622 trial focused on determining the safety and feasibility of substituting the second generation dual ABL/SRC kinase inhibitor, dasatinib (60 mg/m^2/day), to the same intensive chemotherapy backbone used in the previous AALL0031 trial.[17] Dasatinib was 300 times as potent as imatinib in blocking BCR/ABL1 in vitro,[19] active in patients with imatinib resistant clones,[20] and the sole TKI available that crossed the blood-brain barrier.[21] In the AALL0622 study, patients received dasatinib in all blocks of chemotherapy starting at day 15 of induction therapy. CR rates and undetectable end-induction MRD levels were higher on the AALL0622 trial than the predecessor AALL031 trial on which imatinib was started postinduction. This suggested that beginning TKI therapy during induction leads to better early response. Toxicity in AALL0622 was similar to AALL0031. On AALL0622, matched sibling transplants were recommended if available, and well-matched unrelated transplants allowed in high-risk patients based on elevated MRD levels (discussed later). A total of 30% met the criteria for transplant, 15% had a matched sibling, and 15% were high risk based on MRD levels. No significant difference in outcomes was apparent between patients undergoing transplant and those receiving chemotherapy plus dasatinib. Despite its better CNS penetrance, dasatinib did not completely prevent CNS relapses.[17] Ultimately, the EFS of the two trials were similar, suggesting no significant differences between imatinib and dasatinib at the doses used in these studies in preventing relapses in newly diagnosed pediatric Ph+ ALL.

2.2 | More recently completed trials

AALL0622 was terminated early in order to open the first transatlantic Ph+ ALL trial, COG AALL1122 (BMS CA180372), conducted jointly by COG, EsPhALL, and Bristol Myers Squibb, the manufacturer of dasatinib. AALL1122 tested the combination of dasatinib (60 mg/m^2/day) added to the EsPhALL chemotherapy backbone. This backbone was selected because it had significantly lower cumulative doses of cyclophosphamide, ifosfamide, and etoposide, and therefore a potentially lower risk of late effects, such as infertility and secondary malignancy than the COG AALL0031/AALL0622 backbone. Early results from COG AALL1122 have been reported in abstract form (Table 1),[22] with publication of longer term outcome data expected in the near future.

Following completion of the randomized testing of imatinib, the EsPhALL trial was expanded (EsPhALL2010) with all patients receiving continuously dosed imatinib, starting on induction day 15, plus the intensive EsPhALL chemotherapy backbone with HSCT reserved for high-risk patients defined by early response. The outcome of EsPhALL2010 was similar to the prior trial conducted by this group (EsPhALL2004), although far fewer patients underwent HSCT on the 2010 trial (40% vs 80% on the predecessor trial).[23] See Table 1 for a summary of outcomes in Ph+ ALL trials in children, adolescents, and young adults.

The Chinese Children's Cancer Group has recently published the results of their CCCG-ALL-2015 Ph+ ALL trial that randomized patients to receive imatinib (300 mg/m^2/day) or dasatinib (80 mg/m^2/day) added to a modified St Jude Total XV/XVI backbone.[24] This trial showed a significantly better outcome in the dasatinib arm with improved EFS, OS, and decreased relapse rate. Follow up is relatively short (median 26.4 months) and the results of the imatinib arm appear inferior to those reported previously by the COG and EsPhALL. While further follow up is needed, this trial suggests advantages to using higher doses of dasatinib in Ph+ ALL than tested in the COG AALL0622 and combined EsPhALL/COG AALL1122 trials.

TABLE 1 Pediatric clinical trials for Ph+ acute lymphoblastic leukemia

Trial	Years (# patients)	Chemotherapy backbone	TKI	cXRT	HSCT	Relapse rate BM/(PB) iCNS BM + CNS other	EFS	OS
COG AALL0031[15,16]	2002-2006 (54)	AALL0031	Imatinib	All	43%	23% 7% 0% 0%	5 years: 68%	5 years: 81%
EsPhALL2004[14]	2004-2009 (178)	BFM HR	Imatinib	All	81%	13% 0% 7% (BM + other) 2%	5 years: 60%	5 years: 72%
COG AALL0622[18]	2008-2012 (60)	AALL0031	Dasatinib	*CNS3 only*	32%	25% 7% 3% 1%	5-y: 60%	5-y: 86%
EsPhALL2010[23]	2010-2014 (155)	BFM HR	Imatinib	All	38%	14% 4% 8% 0%	5 years: 57%	5 years: 72%
EsPhALL/COG AALL1122[22]	2012-2014 (106)	BFM HR	Dasatinib	*CNS3 only*	14%	20% 4% 4% 4%	3 years: 65.5%	3 years: 91.5%

Abbreviations: cXRT, cranial radiation; TKI, tyrosine kinase inhibitor.

2.3 | Ongoing trials

Because Ph+ ALL is a rare disease in children, completing phase 2 trials on a single continent takes many years to be feasible, and international collaboration is required to perform phase 3 trials. The COG and EsPhALL groups collaborated to develop the EsPhALL2017/COG AALL1631 trial (NCT03007147). For standard-risk patients, defined as those with low MRD ($<5 \times 10^{-4}$) at the end of the second block of chemotherapy, about week 12 of treatment, the trial compares outcomes and toxicity of imatinib added to one of two chemotherapy backbones, the EsPhALL backbone or a less intensive backbone similar to what high-risk ALL Ph-negative patients receive on COG trials.[25,26] The goal is to minimize short-term and long-term toxicity while maintaining or improving cure rates. High-risk patients, defined by slow response at a single time point (MRD $\geq 5 \times 10^{-4}$ after 10-12 weeks of therapy), are treated initially on the EsPhALL backbone but are allocated to allogeneic HSCT; for these patients, the study aims to determine the feasibility of administering post-HSCT imatinib.

2.4 | Timing of TKI introduction

A common question in newly diagnosed patients is when to start TKI therapy? In AALL0031 and the original EsPhALL trial, the TKI was started after completion of 4 weeks of induction,[14,15] whereas on AALL0622, EsPhALL2010, and the joint EsPhALL/COG AALL1122 trial, it was started on induction day 15.[17,22,27] As noted above, starting TKI earlier clearly led to better early responses.[17,23] A day 15 start was chosen to provide uniformity in the patients on trial and also give enough time for results of *BCR-ABL1* fusion testing to become available. Testing for *BCR-ABL1* is rapidly available today in most high-income countries. Therefore, TKI can and should be started safely as soon as a patient is known to have Ph+ ALL, as is allowed in the current EsPhALL2017/COG AALL1631 trial and was done in the CCCG-ALL-2015 trial.[24]

2.5 | Choosing a TKI

Today, both imatinib and dasatinib are approved in North America, Canada, and Europe for use in newly diagnosed children with Ph+ ALL. Dasatinib crosses the blood-brain barrier and theoretically provides better CNS protection than imatinib. CNS relapse rates have ranged from 7 to 11% at 5 years with imatinib[14,17,23] and 4 to 15% with dasatinib at 3-5 years. Results of nonrandomized trials performed by COG and EsPhALL have not shown any obvious differences in outcomes with the two TKIs at the doses tested (Table 1). The St Jude group has safely used a higher dose of dasatinib (80 mg/m^2/day).[28] This dose was tested in the randomized CCCS-ALL-2105 trial[24] and shown to provide superior results to imatinib (300 mg/m^2/day). Longer follow up is needed to determine whether the outstanding early outcome with higher dose dasatinib will be maintained. Also, it is not clear whether the dose of dasatinib tested would prove to be superior to the higher doses of imatinib used in previous COG and currently accruing combined COG/EsPhALL trials (340 mg/m^2/day). Therefore, at this time, either imatinib (300-340 mg/m^2/day)[14-17,23,27] or dasatinib (60-80 mg/m^2/day)[17] are

TABLE 2 Comparison of tyrosine kinase inhibitors for Ph$^+$ acute lymphoblastic leukemia

Tyrosine kinase inhibitor	Idiosyncratic side effect	Tested in combination with chemotherapy in adults	Tested in combination with chemotherapy in children	Crosses blood-brain barrier	Effective in T315I mutation
Imatinib	Liver toxicity during maintenance requiring discontinuous dosing in pediatric trials Low risk of QTc prolongation	Yes	Yes	No	No
Dasatinib	Pleural effusions when given at higher doses Prolonged QTc	Yes	Yes	Yes	No
Nilotinib	Pruritis, headache Nausea Fatigue Elevated lipase Hypertriglyceridemia Prolonged QTc	Yes	No	No	No
Ponatinib	Pancreatitis, hypertension Arterial thrombosis Pleural and pericardial effusions, cardiac arrhythmias Low risk of QTc prolongation	Yes	No	No	Yes

reasonable choices to use along with chemotherapy to treat newly diagnosed Ph$^+$ ALL patients. Other ABL-class TKIs such as nilotinib,[29] bosutinib,[30] and ponatinib[31] do not yet have an established safety profile when combined with chemotherapy in children, but could be considered in relapsed patients with demonstrated resistance to imatinib and dasatinib. See Table 2 for list of TKIs and their attributes.

2.6 | Choosing a chemotherapy backbone

The optimal postinduction chemotherapy backbone for children and young adults with Ph$^+$ ALL has not been determined. COG established an effective chemotherapy backbone that, when combined with imatinib (COG AALL0031) or dasatinib (COG AALL0622), led to a long-term EFS rate between 60 and 70%.[16,17] However, as mentioned above, this chemotherapy regimen includes high cumulative doses of chemotherapy associated with an increased risk of damaging long-term side effects. More patients have been treated on clinical trials with the EsPhALL regimen, and this serves as the "standard" arm of the current joint EsPhALL2017/COG AALL1631 trial. Cumulative chemotherapy doses associated with significant late effects are lower on that backbone. However, a significant concern with the EsPhALL backbone is treatment-related mortality, particularly in the three high-risk consolidation blocks that combine high-dose dexamethasone and intensive chemotherapy.[14,23] Patients need to be monitored very closely during these blocks, and supportive care measures (antimicrobial prophylaxis, use of filgrastim, or other stem cell growth factors) are strongly advised. Ultimately, given that EFS and OS rates are similar, either the EsPhALL or COG backbone is a reasonable choice, and either could be considered "standard of care."

2.7 | How to handle toxicities

Imatinib and dasatinib have been generally well tolerated in combination with chemotherapy. In the face of delays due to myelosuppression, we generally continue TKI for 2 weeks before stopping. During maintenance therapy, mercaptopurine and methotrexate are held first prior to holding imatinib or dasatinib. In the setting of myelosuppression after bone marrow transplant, TKI should be held until counts recover. TKI should be held during serious infections, in the setting of hepatic toxicity manifested by transaminase elevations >20 times normal with elevated direct bilirubin more than 1.5 times normal. In the setting of a grade 1 prolonged corrected QT interval (QTc), other medications causing prolonged QTc should be preferentially discontinued, but with grade 2 or higher, TKI should be held. Both dasatinib and imatinib can cause effusions. If an effusion is thought to be due to the TKI, the agent should be held and restarted at 80% the original dose.

2.8 | Identifying high-risk patients

Detection of MRD has been an effective way to identify patients with ALL who have an increased risk of relapse.[32-37] Many groups consider ALL patients who remain MRD positive after 3-4 months of therapy to be at very high risk of relapse, and appropriate candidates for HSCT in CR1 or other experimental therapies.

The prognostic significance of MRD measurements in patients with Ph$^+$ ALL receiving TKI therapy was demonstrated on the EsPhALL2004 trial.[38] Of nine patients with negative MRD at the end of the first month of treatment (induction IA), none relapsed. Patients who had detectable MRD after induction IA but negative MRD by the end of second phase (induction phase IB, week 12) had a relatively low

5-year cumulative incidence (CI) of relapse of 14.3%. Those who had detectable MRD, either at a low ($<5 \times 10^{-4}$) or high level ($\geq 5 \times 10^{-4}$) had a higher 5-year CI of relapse (35.3 and 43.1%, respectively). These results provide the rationale for risk stratification on the current joint COG/EsPhALL protocol, which uses end-consolidation phase IB Ig/TCR MRD levels to classify patients as either standard or high risk.

In addition to flow cytometry and Ig/TCR PCR, another method to measure MRD in Ph$^+$ ALL is quantitative reverse transcriptase PCR (qRT-PCR) of *BCR-ABL1* transcript expression. In the EsPhALL2004 trial, the level of concordance between the *BCR-ABL1* transcript levels and Ig/TCR MRD levels was 65-71% depending on the time point it was obtained. In fact, when samples were compared, MRD levels based on *BCR-ABL1* transcript tended to be higher than when measured by IG/TCR methods, and was generally less reliable in predicting outcomes.[38] In the joint EsPhALL/COG trial AALL1122, MRD was assessed by Ig/TCR PCR, with flow cytometry, and qRT-PCR of *BCR-ABL1* serving as backup tests. HSCT recommendations could be made for 98% of patients by flow cytometry, 84% by Ig/TCR PCR, and only 39% of patients by *BCR-ABL1* PCR, primarily because assay-specific requirements were not met.[39] MRD results were concordant 90% of the time between the Ig/TCR PCR and flow cytometry assays. Although concordance rates were similar for *BCR-ABL1* PCR, results were unavailable for the majority of the patients making this method impractical. PCR for *BCR-ABL1* was not as reliable as flow cytometry as a backup test.

For patients not enrolled on a clinical trial, using flow cytometry for MRD assessment is perhaps the most practical method in North American centers. This method will lead to a usable result in nearly all patients with Ph$^+$ ALL. Next-generation sequencing of clonotypic Ig/TCR rearrangements is another methodology that can detect lower levels of residual disease than flow cytometry, but it has not yet been evaluated in Ph$^+$ ALL.[41] Other markers of high-risk disease, such as deletions of the *Ikaros zinc finger 1 gene* (*IKZF1*)[42,43] observed in 60-70% of pediatric Ph$^+$ ALL patients, continue to be tested in clinical trials, and may ultimately augment MRD-based risk classification.[17]

3 | CASE 1 CONTINUED

At the end of induction, MRD was determined via flow cytometry and found to be undetectable (<0.01%). However, FISH showed that 18% of cells had *BCR-ABL1* fusion. Further molecular studies revealed that the patient had the p210 form of BCR-ABL1.

3.1 | CML in blast crisis can masquerade as Ph$^+$ ALL

A variation of the scenario described above occurs in a small number of patients with Ph$^+$ ALL (2/59 or 3% of patients on AALL0622)[17] and can be very confusing to clinicians. In fact, this scenario is what is seen when a patient with CML in blast crisis has successfully achieved control of their blast population but has not yet achieved a molecular remission.[44]

Molecular studies looking at which specific fusion protein is present in the patient can be helpful. Almost all patients with CML have the larger p210 variant of BCR-ABL1, which is the result of the breakpoint in the *BCR* gene occurring in the major breakpoint cluster region (M-BCR). In Ph$^+$ ALL, most patients have a breakpoint within the minor breakpoint cluster region (m-BCR) leading to a smaller mBCR-ABL transcript that encodes a p190 protein.[45,46] However, the p210 transcript is present in 10-15% of pediatric cases of de novo Ph$^+$ ALL and is not by itself enough to support the diagnosis of CML.[46]

The FISH-positivity in nonleukemic cells at the end of induction provides the strongest evidence of the underlying diagnosis of CML. Because CML is a stem cell disease and blast crisis is associated with a higher risk of relapse, we recommend that patients with suspected CML in blast crisis undergo HSCT, preferably after obtaining a major molecular response. Patients thought to have Ph$^+$ ALL at initial diagnosis treated without HSCT have been described who later relapse in chronic phase CML.[44]

Recently, researchers in Prague sought to understand better discrepancies between MRD levels measured by Ig/TCR PCR, a genomic assay, with qRT-PCR determination of MRD via measuring *BCR-ABL1* transcript expression. To address this problem, they developed a DNA-based assay to measure *BCR-ABL1* genomic copies and found that the discrepancies persisted. In fact, nearly 20% of patients with ALL and a p190 fusion and 12.5% of patients with the p210 fusion had discrepant results for the *BCR-ABL1* genomic rearrangement and Ig/TCR PCR. They demonstrated that these patients had *BCR-ABL1* fusion in their nonblast myeloid cells, B cells, and T cells, suggesting that they have CML-like biology with the translocation occurring in a stem cell or multipotent progenitor cell. Interestingly among those with the CML-like biology, 10 of 12 transplanted patients were alive, compared with one of three nontransplanted patients, with a median follow up of 10 years.[40]

3.2 | What to do with low-level persistent *BCR-ABL1* transcript expression

How to manage a patient who shows persistence of low-level *BCR-ABL1* expression by qRT-PCR with negative MRD measured by flow cytometry and/or Ig/TCR MRD is a difficult issue. Sometimes *BCR-ABL1* transcript levels disappear, reappear, and disappear again later in therapy, but the prognostic implications of these findings are unknown. Because transcript levels have not been routinely followed throughout therapy on pediatric studies, we do not yet have a data-driven way to approach this problem. Caution is urged on acting on low-level *BCR-ABL1*-positive PCR results late in therapy.

3.3 | Use of TKI beyond the end of chemotherapy or HSCT

Adults with Ph$^+$ ALL frequently remain on TKI therapy indefinitely, even following HSCT. In addition to the significantly high cost, these

medications cause problems with linear growth and osteopenia when used chronically.[47] In contrast to how these medications are used in adults, pediatric studies show that TKI therapy after the end of chemotherapy treatment is not necessary for cure in the majority of pediatric patients.[14,15,17] Studies have not been done to test the benefit of continuing chemotherapy beyond 2 years in pediatric and young adults with Ph$^+$ ALL. There are conflicting data regarding the utility of post-HSCT TKI administration in Ph$^+$ ALL. In a retrospective analysis of 473 adult Ph$^+$ ALL patients transplanted in CR1, post-HSCT TKI administration (primarily imatinib) was associated with a more favorable DFS on multivariate analysis; it was also associated with a lower CI of acute GVHD.[48] However, a CIBMTR analysis of TKI maintenance after HSCT for adult CML demonstrated no survival benefit.[49] Thus, currently available data does not definitively support the use of prophylactic TKI post-HSCT. The current EsPhALL2017/COG AALL1631 trial is studying the feasibility of post-transplant TKI in high-risk Ph$^+$ ALL patients.

4 | CASE 2

A 15-year-old male with Ph$^+$ ALL was treated with dasatinib plus chemotherapy according to AALL0622. He remained in remission for 3 years post-HSCT, at which point he had a bone marrow relapse. He was treated with a four-drug reinduction plus dasatinib 100 mg/day (60 mg/m^2/day). He now had six copies of *BCR-ABL1* detected via FISH in each cell rather than one, but no BCR-ABL1 point mutations. We increased his dose of dasatinib to 140 mg/day (87.5 mg/m^2/day) based on standard adult dosing. He achieved remission and was successfully transplanted using his fully matched brother as a donor.

4.1 | Therapy in relapsed Ph$^+$ ALL patients

In spite of being heavily pretreated, many patients with relapsed Ph$^+$ ALL have been successfully salvaged through reinduction and consolidation followed by HSCT, especially those who did not receive HSCT in CR1. For example, the 5-year OS on the AALL00622 trial was 86% compared with EFS of 60%, demonstrating that many patients can be salvaged after relapse.[17] In fact, at relapse, many patients can achieve remission with relatively little chemotherapy including a TKI combined with three-drug reinduction without anthracyclines. The efficacy of prednisone plus TKI has been demonstrated in elderly patients with Ph$^+$ ALL,[50] and researchers have proposed combining blinatumomab plus TKI in a chemotherapy-free approach in this population.[51]

In choosing a TKI, it is important to look for *BCR-ABL1* amplification, which can be overcome by providing higher doses of imatinib or dasatinib. Alternatively, specific point mutations in *BCR-ABL1* can cause absolute or relative resistance to imatinib and/or dasatinib by blocking the ability of these medications to bind to BCR-ABL1. In contrast to adults, the vast majority of children with Ph$^+$ ALL do not develop point mutations even at relapse, possibly due to the more intensive chemotherapy backbones used for pediatric Ph$^+$ ALL.[17,52] All patients should have cytogenetics and resistance testing sent at the time of relapse or progression. Most patients maintain sensitivity to imatinib or dasatinib, and it is reasonable to restart the same TKI the patient had previously while waiting for results of resistance testing. The TKI can be changed based on the results of these analyses, if needed. When transplanting relapsed patients, TBI-based regimens should be used in patients not previously transplanted. Options for a patient who has already had a TBI-based transplant would be a second transplant with an alternative donor or chimeric antigen receptor (CAR) T-cell therapy.[53]

5 | SUMMARY

Targeted therapy has revolutionized the treatment of Ph$^+$ ALL. This disease has gone from one of the least curable forms of childhood ALL to a disease with overall survival rates approaching those of other ALL subtypes. New drugs such as ponatinib targeting mutant BCR-ABL1, the allosteric BCR-ABL1 inhibitor ascminib,[54] as well as immunotherapy using blinatumomab, inotuzumab, or CAR T-cell therapy may improve our ability to cure these patients while reducing the long-term treatment-related side effects.

CONFLICT OF INTEREST

Kirk R. Schultz is a paid Data Safety and Monitoring Board member for Juno Therapeutics/Celgene owned by Bristol Meyer Squibb. Stephen P. Hunger has received honoraria/consulting fees from Novartis and Amgen and owns stock in Amgen. Lewis B. Silverman has received consulting fees from Servier, Takeda, and Syndax. William B. Slayton has received honoraria and travel from Jazz Pharmaceuticals.

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REFERENCES

1. Conter V, Arico M, Basso G, et al. Long-term results of the Italian Association of Pediatric Hematology and Oncology (AIEOP) Studies 82, 87, 88, 91 and 95 for childhood acute lymphoblastic leukemia. *Leukemia*. 2010;24:255-264.
2. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol*. 2012;30:1663-1669.
3. Kamps WA, van der Pal-de Bruin KM, Veerman AJ, et al. Long-term results of Dutch Childhood Oncology Group studies for children with acute lymphoblastic leukemia from 1984 to 2004. *Leukemia*. 2010;24:309-319.
4. Moricke A, Zimmermann M, Reiter A, et al. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. *Leukemia*. 2010;24:265-284.
5. Pui CH, Pei D, Sandlund JT, et al. Long-term results of St Jude Total Therapy Studies 11, 12, 13A, 13B, and 14 for childhood acute lymphoblastic leukemia. *Leukemia*. 2010;24:371-382.
6. Arico M, Valsecchi MG, Camitta B, et al. Outcome of treatment in children with Philadelphia chromosome-positive acute lymphoblastic leukemia. *N Engl J Med*. 2000;342:998-1006.

7. Arico M, Schrappe M, Hunger SP, et al. Clinical outcome of children with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia treated between 1995 and 2005. *J Clin Oncol*. 2010;28:4755-4761.
8. Bernt KM, Hunger SP. Current concepts in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia. *Front Oncol*. 2014;4:54.
9. Bleckmann K, Schrappe M. Advances in therapy for Philadelphia-positive acute lymphoblastic leukaemia of childhood and adolescence. *Br J Haematol*. 2016;172:855-869.
10. Ottmann OG, Druker BJ, Sawyers CL, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. *Blood*. 2002;100:1965-1971.
11. de Labarthe A, Rousselot P, Huguet-Rigal F, et al. Imatinib combined with induction or consolidation chemotherapy in patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: results of the GRAAPH-2003 study. *Blood*. 2007;109:1408-1413.
12. Thomas DA, Faderl S, Cortes J, et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. *Blood*. 2004;103:4396-4407.
13. Yanada M, Takeuchi J, Sugiura I, et al. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group. *J Clin Oncol*. 2006;24:460-466.
14. Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. *Lancet Oncol*. 2012;13:936-945.
15. Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. *J Clin Oncol*. 2009;27:5175-5181.
16. Schultz KR, Carroll A, Heerema NA, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. *Leukemia*. 2014;28:1467-1471.
17. Slayton WB, Schultz KR, Kairalla JA, et al. Dasatinib plus intensive chemotherapy in children, adolescents, and young adults with Philadelphia chromosome-positive acute lymphoblastic leukemia: results of Children's Oncology Group trial AALL0622. *J Clin Oncol*. 2018;36:2306-2314.
18. Bowman WP, Larsen EL, Devidas M, et al. Augmented therapy improves outcome for pediatric high risk acute lymphocytic leukemia: results of Children's Oncology Group trial P9906. *Pediatr Blood Cancer*. 2011;57:569-577.
19. O'Hare T, Walters DK, Stoffregen EP, et al. In vitro activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. *Cancer Res*. 2005;65:4500-4505.
20. Carter TA, Wodicka LM, Shah NP, et al. Inhibition of drug-resistant mutants of ABL, KIT, and EGF receptor kinases. *Proc Natl Acad Sci USA*. 2005;102:11011-11016.
21. Porkka K, Koskenvesa P, Lundan T, et al. Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. *Blood*. 2008;112:1005-1012.
22. Hunger SP, Saha V, Devidas M, et al. CA180-372: an international collaborative phase 2 trial of dasatinib and chemotherapy in pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). *Blood*. 2017;130:98.
23. Biondi A, Gandemer V, De Lorenzo P, et al. Imatinib treatment of paediatric Philadelphia chromosome-positive acute lymphoblastic leukaemia (EsPhALL2010): a prospective, intergroup, open-label, single-arm clinical trial. *Lancet Haematol*. 2018;5:e641-e652.
24. Shen S, Chen X, Cai J, et al. Effect of dasatinib vs imatinib in the treatment of pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: a randomized clinical trial. *JAMA Oncol*. 2020;6(3):358-366.
25. Larsen EC, Devidas M, Chen S, et al. Dexamethasone and high-dose methotrexate improve outcome for children and young adults with high-risk B-acute lymphoblastic leukemia: a report from children's oncology group study AALL0232. *J Clin Oncol*. 2016;34:2380-2388.
26. Salzer WL, Burke MJ, Devidas M, et al. Toxicity associated with intensive postinduction therapy incorporating clofarabine in the very high-risk stratum of patients with newly diagnosed high-risk B-lymphoblastic leukemia: a report from the Children's Oncology Group study AALL1131. *Cancer*. 2018;124:1150-1159.
27. Biondi A, Cario G, De Lorenzo P, et al. Long-term follow up of pediatric Philadelphia positive acute lymphoblastic leukemia treated with the EsPhALL2004 study: high white blood cell count at diagnosis is the strongest prognostic factor. *Haematologica*. 2019;104:e13-e16.
28. Jeha S, Coustan-Smith E, Pei D, et al. Impact of tyrosine kinase inhibitors on minimal residual disease and outcome in childhood Philadelphia chromosome-positive acute lymphoblastic leukemia. *Cancer*. 2014;120:1514-1519.
29. Kim DY, Joo YD, Lim SN, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. *Blood*. 2015;126:746-756.
30. Redaelli S, Piazza R, Rostagno R, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. *J Clin Oncol*. 2009;27:469-471.
31. Jabbour E, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. *Lancet Oncol*. 2015;16:1547-1555.
32. Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta-analysis. *JAMA Oncol*. 2017;3(7):e170580.
33. Borowitz MJ, Devidas M, Hunger SP, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. *Blood*. 2008;111:5477-5485.
34. Borowitz MJ, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. *Blood*. 2015;126:964-971.
35. Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. *Blood*. 2010;115:3206-3214.
36. Schrappe M, Valsecchi MG, Bartram CR, et al. Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study. *Blood*. 2011;118:2077-2084.
37. Zhou J, Li A, Goldwasser MA, et al. Quantitative analysis of minimal residual disease at the completion of induction therapy predicts relapse in children with B-lineage acute lymphoblastic leukemia in DFCI ALL Consortium Protocol 95-01. *Blood*. 2004;104:323.
38. Cazzaniga G, De Lorenzo P, Alten J, et al. Predictive value of minimal residual disease in Philadelphia-chromosome-positive acute lymphoblastic leukemia treated with imatinib in the European intergroup study of post-induction treatment of Philadelphia-chromosome-positive acute lymphoblastic leukemia, based on immunoglobulin/T-cell receptor and BCR/ABL1 methodologies. *Haematologica*. 2018;103:107-115.
39. Reshmi S, Stonerock E, Borowitz M, et al. International laboratory comparison of methodologies for determining minimal residual

disease (MRD) in childhood Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). *Blood*. 2015;126:2612.
40. Hovorkova L, Zaliova M, Venn NC, et al. Monitoring of childhood ALL using BCR-ABL1 genomic breakpoints identifies a subgroup with CML-like biology. *Blood*. 2017;129:2771-2781.
41. Ladetto M, Bruggemann M, Monitillo L, et alNext-generation sequencing and real-time quantitative PCR for minimal residual disease detection in B-cell disorders. *Leukemia*. 2014;28:1299-1307.
42. Qazi S, Uckun FM. Incidence and biological significance of IKZF1/Ikaros gene deletions in pediatric Philadelphia chromosome negative and Philadelphia chromosome positive B-cell precursor acute lymphoblastic leukemia. *Haematologica*. 2013;98:e151-e152.
43. van der Veer A, Zaliova M, Mottadelli F, et al. IKZF1 status as a prognostic feature in BCR-ABL1-positive childhood ALL. *Blood*. 2014;123:1691-1698.
44. Kolenova A, Maloney KW, Hunger SP. Philadelphia chromosome-positive acute lymphoblastic leukemia or chronic myeloid leukemia in lymphoid blast crisis. *J Pediatr Hematol Oncol*. 2016;38:e193-e195.
45. Kelliher M, Knott A, McLaughlin J, et al. Differences in oncogenic potency but not target cell specificity distinguish the two forms of the BCR/ABL oncogene. *Mol Cell Biol*. 1991;11:4710-4716.
46. Suryanarayan K, Hunger SP, Kohler S, et al. Consistent involvement of the bcr gene by 9;22 breakpoints in pediatric acute leukemias. *Blood*. 1991;77:324-330.
47. Jaeger BA, Tauer JT, Ulmer A, et al. Changes in bone metabolic parameters in children with chronic myeloid leukemia on imatinib treatment. *Med Sci Monit*. 2012;18:CR721-CR728.
48. Brissot E, Labopin M, Beckers MM, et al. Tyrosine kinase inhibitors improve long-term outcome of allogeneic hematopoietic stem cell transplantation for adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia. *Haematologica*. 2015;100:392-399.
49. DeFilipp Z, Ancheta R, Liu Y, et al. Maintenance tyrosine kinase inhibitors following allogeneic hematopoietic stem cell transplantation for chronic myelogenous leukemia: a center for international blood and marrow transplant research study. *Biol Blood Marrow Transplant*. 2019.
50. Vignetti M, Fazi P, Cimino G, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. *Blood*. 2007;109:3676-3678.
51. Papayannidis C, Martinelli G. Blinatumomab in Ph+ B-ALL: present and perspectives. *Oncotarget*. 2017;8:93309-93310.
52. Chang BH, Willis SG, Stork L, et al. Imatinib resistant BCR-ABL1 mutations at relapse in children with Ph+ ALL: a Children's Oncology Group (COG) study. *Br J Haematol*. 2012;157:507-510.
53. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med*. 2014;371:1507-1517.
54. Hughes TP, Mauro MJ, Cortes JE, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. *N Engl J Med*. 2019;381:2315-2326.

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