Treatment of Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia in Adults: A Broader Range of Options, Improved Outcomes, and More Therapeutic Dilemmas

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OVERVIEW

The article addresses selected key areas of flux in the management of Philadelphia chromosome–positive acute lymphoblastic leukemia. There is no doubt that tyrosine kinase inhibitors (TKIs) have made a major contribution to higher rates of complete remission and that more patients are now surviving long term. Many patients tolerate TKIs well, and remission can be achieved with minimal toxicity. Because remissions can include a proportion of patients who become BCR-ABL transcript negative, the question of whether allogeneic hematopoietic stem cell transplantation can be avoided requires discussion. Despite the major progress that has been made and the relative profusion of therapeutic choice compared with 10 years ago, evidence is still lacking for many of the major possible interventions, and how to combine them is unclear. Because of the rarity of the condition and the enticing possibility of increasing traction to therapy, clinical trials and international cooperation remain paramount.

Acute lymphoblastic leukemia (ALL) in which the Philadelphia (Ph) chromosome t(9;22) is detected (i.e., Ph+ ALL) is a genetically, biologically, and clinically distinct subtype of B-precursor ALL, and it comprises approximately 20% of the total ALL incidence. The incidence of Ph+ ALL increases with age, from less than 5% in younger children to 20% to 25% in older adults, although population-based studies indicate that the incidence does not continue to increase beyond the fourth decade. Standard ALL chemotherapy treatment alone results in a complete remission (CR) rate of at least 10% lower than in Ph-negative ALL, with a median survival of around 8 months. However, in recent years, the addition of TKIs to remission induction treatment—combined with earlier and more frequent allogeneic donor identification, facilitating allogeneic hematopoietic stem cell transplantation (alloHSCT)—has made a considerable change to the outcome. However, the relatively rapid expansion of the range of realistic therapeutic possibilities in an uncommon disease has generated some genuine therapeutic dilemmas in an arena where testing all of the possibilities in well-designed trials has not yet occurred. Furthermore, there is international variability and even local variability in the availability of some of the therapeutic options and of what may be considered standard-of-care choices in some geographic locations is not relevant to others. In this summary, I will focus on key decision points in the treatment of Ph+ ALL, posing the relevant therapeutic questions and evaluating evidence that supports common approaches. I will highlight areas in which there is no clear best practice, providing my personal opinion only when no prevailing consensus exists.

WHAT ARE THE KEY POINTS IN THE PRETREATMENT WORK-UP?

This is a rare disease. As many patients as possible should be offered the opportunity for referral to a major treatment center as soon as possible when ALL is suspected. Even so, diagnostic adequate work-up for Ph+ ALL is straightforward and within the reach of most centers. All patients with ALL should be evaluated urgently for the presence of the Ph chromosome by conventional cytogenetics, fluorescent in situ hybridization, and reverse transcriptase polymerase chain reaction (RT-PCR) for BCR-ABL p190 and p210 transcripts. The absolute number of BCR-ABL transcripts should be quantified relative to a housekeeping gene, usually GUS or ABL, using real-time quantitative PCR. p210 quantification is standardized internationally because of its routine use in chronic myeloid leukemia (CML) monitoring, whereas p190 quantification is not standardized, and interlaboratory variation in methods and results can occur. ABL kinase domain mutations at diagnosis that are likely to render resistance to TKIs have been identified by deep sequencing, but they typically are not detected by current conventional ap-
proaches. Because their clinical significance is undetermined, they currently cannot be used to direct initial therapy.

**HOW TO INDUCE COMPLETE REMISSION IN PH+ ALL**

Traditional chemotherapy regimens result in a low CR rate and poor outcome, but, despite the lack of randomized studies over the past 10 years, overwhelming evidence of a higher rate of CR and a long-term survival benefit with the addition of TKIs to chemotherapy regimens has emerged. Most of these studies have been conducted with imatinib at doses between 400 mg and 800 mg daily. The German Multicenter Acute Lymphoblastic Leukemia (GMALL) study evaluated imatinib alternating with or concurrent to induction chemotherapy in 92 patients who had de novo Ph+ ALL. CR was achieved in 95% of patients, and the 2-year overall survival (OS) rate was 36%.9 The University of Texas MD Anderson Cancer Center (MDACC) used a hyperCVAD regimen in combination with imatinib in patients with de novo or minimally treated Ph+ ALL, resulting in 3-year OS rate of 54%.10 Yanada et al11 reported CR rates of 96% in 80 patients (70% achieved BCR-ABL1 transcript negativity) compared with 51% in historic controls.11 The 1-year event-free survival (EFS) and OS rates were 60% and 76%, respectively. The Northern Italian Leukemia Group (NILG) reported a CR rate of 92% in 59 patients with newly diagnosed Ph+ ALL using short pulses of an imatinib/chemotherapy combination; 5-year OS and disease-free survival (DFS) rates were 38% and 39%, respectively, compared with 23% and 25%, respectively, in historic controls.12 The U.K. ALL12/E2993 study13 was the most recent to report and was the largest of its type (175 patients treated with imatinib added to standard therapy and compared with a large historic cohort of 266 patients treated on the same trial in the preimatinib era). The study showed a considerable survival advantage for an imatinib-containing regimen. The earlier addition of imatinib during therapy resulted in the best outcome.3 The data are discussed in more detail later in this chapter. There is no rationale now for treating Ph+ ALL without a TKI.

**WHICH TKI IS OPTIMAL FOR FRONT-LINE THERAPY?**

Studies reporting the use of a TKI other than imatinib as front-line therapy are in the minority,14,15 but some studies are ongoing (e.g., the European Working Group on ALL study of dasatinib and chemotherapy induction in older persons16). There are theoretical differences between the TKIs in BCR-ABL1 kinase domain binding, potency of BCR-ABL1 kinase inhibition (e.g., nilotinib and dasatinib are more potent than imatinib), and activity against non–tyrosine kinases (e.g., dasatinib is active against SRC kinases). Ponatinib has potential activity against polymutant BCR-ABL1 alleles, which occur (at least in CML) after the progressive exhaustion of the pool of unmutated BCR-ABL1 alleles over the course of sequential TKI therapy.17 Researchers at the MDACC have evaluated and published data from sequential trials with imatinib,18 dasatinib,14 and ponatinib, a potent pan–BCR-ABL1 TKI,18 each in combination with hyperC-VAD, with no clearly elucidated difference between them to date. No direct comparison has been evaluated, and—to my knowledge—no ongoing clinical study is addressing the question of which is the best initial TKI. I would like to direct the readers to well-researched and carefully concluded evidence-based guidelines for TKI use in ALL, which have recently delineated the Canadian perspective on this matter and which provide more detail than can be given here.19

**CAN PH+ ALL BE TREATED WITHOUT CHEMOTHERAPY?**

Induction chemotherapy for ALL is not without toxicity; a number of patients, regrettably, succumb to complications. Sepsis during the neutropenic period of induction therapy is a common precursor to serious morbidity and mortality. Mortality varies with age but is rarely less than 5%20,21 and can be as high as 15% to 20% in older people.21,22 Vignetti et al23 were the first to report data on chemotherapy-free induction therapy for Ph+ ALL.23 The LAL0201-B trial from the Gruppo Italiano Malattie Ematologiche dell’Adulto (GIMEMA) study included only patients older than age 60, with a median age of 69. Imatinib (800 mg/day) was given with prednisolone. The CR rate was 100%, with minimal toxicity, and the median survival was 20 months, with a 12-month OS of 74%. Postremission therapy and long-term outcomes were not reported. A further study from the same group, GIMEMA LAL1205, showed a similarly high CR rate with no mortality when dasatinib was combined with a corticosteroid alone as induction.15 Interpretation of those studies will be
confounded by the heterogeneous therapy given subsequently. An ongoing trial, GIMEMA LAL 1509, used a similar chemotherapy-free induction with dasatinib and corticosteroid induction treatment, but added chemotherapy and/or alloHSCT for patients who did not reach a sustained complete molecular response (CMR; i.e., no detectable BCR-ABL1 transcripts). This approach has been reported so far only in abstract form, but the results are very interesting. The CR rate was 97%, with no induction-related deaths, which included CMR in 18%. Interestingly, BCR-ABL1 p210 (45% of cases in the report) had a worse prognosis, with lower initial susceptibility to TKIs and a 58% incidence of relapse. The report provocatively suggests that the subset of patients who had deep molecular remissions may be spared further intensive treatment. The long-term follow-up of this study will be of major importance to the field. A recently completed, but also not yet published, study (GRAAPPH-2005) from the French Group for Research on Adult Acute Lymphocytic Leukemia Study (GRAALL) also highlights the value of a lower intensity of chemotherapy during induction. Chalandon et al25 randomly assigned 265 previously untreated patients with Ph+ ALL to receive induction with imatinib/hyperCVAD or imatinib with dexamethasone/vincristine (DIV). Very high CR rates were noted in both arms (DIV, 98%; hyperCVAD, 91%); the lower CR rate in the hyperCVAD arm was a result of higher induction mortality.26 DIV induction was noninferior to hyperCVAD, with no difference in 3-year EFS (46% vs. 38%; p = 0.25) and OS (53% vs. 49%; p = 0.61).

Although the long-term outlook of treating patients without chemotherapy is unknown, this is a reasonable treatment approach in older patients and should be considered. A detailed discussion of the treatment of older people with ALL in general is given in the chapter by Dr. David Marks.

WHAT IS THE MOST APPROPRIATE CNS-DIRECTED THERAPY IN PH+ ALL?

A small proportion of patients with ALL will present with central nervous system (CNS) disease, but all will need prophylaxis. Recent data using sensitive detection of ALL cells in the cerebrospinal fluid (CSF) suggest that higher-than-expected proportion of patients (18%) present with occult ALL cells in the CSF.28 This did not emerge as a clinically relevant problem in the series studies, which suggests that therapy directed at preventing the emergence of CNS disease has been and will remain a very important component of the treatment of ALL. Traditionally, a combination of intrathecal therapy, high-dose systemic therapy that crosses the blood-brain barrier, and irradiation has been used and has resulted in a very low level of CNS relapse. However, CNS relapse, when it does occur, portends a very poor prognosis.29 Typically, patients with Ph+ ALL have been referred for myeloablative HSCT wherever possible and have benefitted from total-body irradiation. However, as we consider chemotherapy-free treatment approaches and reduced-intensity conditioning (RIC) regimens for alloHSCT, the opportunities for CNS-directed prophylaxis to be built-in to the typical protocol are not always obvious. Treating physicians and trialists alike need to consider this issue carefully in an area of practice that does not have a strong evidence base. Imatinib and nilotinib do not cross the blood-brain barrier; dasatinib does and is reportedly part of an effective therapy, and ponatinib has been reported to cross the blood-brain barrier in a murine model.26 However, there are no trial data to support using TKIs as CNS-directed prophylaxis. CNS irradiation now—and rightly—is little used because of toxicity, but it remains unclear whether systemic methotrexate can be dispensed with, even if the approach is a chemotherapy-free one. The clear benefit of high-dose methotrexate on prevention of CNS relapse has never been demonstrated; there is considerable variability in the dose and number of courses used, so there is little firm evidence on which to select this therapeutic component. It may be safest to be assiduous with intrathecal therapy. The total number of intrathecal treatments needed to constitute an appropriate course of therapy is also unclear. However, if patients quickly move from induction to nonmyeloablative alloHSCT, its unlikely they will have had sufficient intrathecal therapy, so resumption after HSCT may be wise.

WHAT IS THE OPTIMAL POSTREMISSION THERAPY? Myeloablative AlloHSCT: Is It Still the Cornerstone of Definitive Therapy for Ph+ ALL?

The cornerstone of postremission therapy for Ph+ ALL traditionally has been myeloablative alloHSCT (reviewed in Fielding31). The strongest support for the overall benefit of sibling alloHSCT in unselected patients with Ph+ ALL comes from the two largest studies conducted in this disease. The LALA-94 trial4 showed that, among 103 patients eligible for HSCT, the availability of a sibling allogeneic donor was independently predictive of remission duration. An analysis of treatment received in the U.K. ALL12/E2993 trial5 in 267 patients showed that patients with Ph+ ALL who received sibling or unrelated donor myeloablative alloHSCT had a much better outcome than those receiving chemotherapy alone. Fewer than 30% of the study population were able to receive allogeneic HSCT, mostly because of older age or failure of existing therapy to generate a CR.

Although any data on the outcome of alloHSCT must be interpreted with caution, because of the problems of selection bias and immortal time bias, the weight of evidence in the pre-TKI era has been interpreted in favor of myeloablative HSCT using either a sibling or unrelated donor in adults with Ph+ ALL who have experienced first complete response (CR1).

CAN WE TREAT PH+ ALL WITHOUT TRANSPLANTATION?

With the advent of the genetically targeted treatment that can generate, at least in a proportion of patients, a negative BCR-ABL1 transcript response, the possibility of dispensing with
allogeneic HSCT, which would be a major advance, must be considered. Evidence in support of this has so far been gathered in patients in whom alloHSCT has not been possible; these patients are never a comparable group to those in whom alloHSCT could be and was performed. Nonrecipients are typically older, have more comorbidities, and are more likely to have experienced relapse by the median time to alloHSCT.5,13

Studies in which alloHSCT was not the primary focus may nonetheless contribute to our understanding of its role. As always, though, the circumstances under which patients did not receive alloHSCT must be taken into account. One of the first studies to suggest omission of alloHSCT as a realistic possibility in the TKI era was a Children’s Oncology Group study in which patients up to age 21 were treated with imatinib added to chemotherapy.32 Postremission treatment with sibling alloHSCT was included in the protocol, but the trial did not allow for matched unrelated donor (MUD) alloHSCT on the basis of a previous, international study in children33 that showed a 43% treatment-related mortality (TRM) for MUD alloHSCT. Hence, this study left a small cohort of children who received an imatinib/chemotherapy combination without alloHSCT. There was relatively high rate of off-protocol MUD alloHSCT that confounded data interpretation. However, at 3 years, the outcomes for those treated with imatinib/chemotherapy (25 patients) compared favorably with those treated with alloHSCT (21 patients); the 3-year DFS without alloHSCT was 85%. Although the study was neither designed nor powered to answer the question of whether imatinib/chemotherapy could replace sibling alloHSCT for children with Ph+, the data introduced the hypothesis that children with Ph+ ALL can be treated successfully without alloHSCT. In combination with emerging data of improved overall outcomes for adults with Ph+ ALL, this study has reasonably sparked consideration of the omission of alloHSCT from treatment. A multivariate analysis of patients treated at the MDACC with hyper-CVAD and TKI regimens,34 which excluded those who had received alloHSCT, revealed that achievement of major molecular response (MMR), namely a BCR-ABL ratio of < 0.1, was associated with better survival outcomes. However, the selection of the MMR as a cutoff remains somewhat arbitrary, although it is explained in the paper, and the numbers of patients on whom this analysis is based are limited. The authors reasonably take the data to support the role of minimal residual disease (MRD) monitoring but wisely do not suggest that these data currently support the omission of alloHSCT.

In my opinion, the most robust evidence to date on the present need to continue considering alloHSCT as a core therapy comes from trials groups that have reported on the outcome of patients who received chemotherapy and a TKI alone and have been able to compare that group with those who received alloHSCT. Among the few published studies to report on the outcome of a substantial group of patients of transplantable age who did not undergo transplantation was the ALL202 trial from the Japanese Adult Leukemia Study Group,13 in which the combination of imatinib and chemotherapy was evaluated in 80 adult patients, 31 of whom did not undergo alloHSCT. When compared with historic controls in whom there were no event-free survivors at 24 months, the 2-year estimated EFS was significantly better for those patients receiving imatinib as part of their therapy. In the largest such study internationally, the Ph+ arm of the U.K. ALL12/E2993 trial examined the outcome of treatment in 266 patients enrolled on the imatinib era and was compared with the outcome in 175 patients receiving the same chemotherapy treatment and alloHSCT approach but with the addition of imatinib.13 There was a large and statistically significant outcome benefit with imatinib cohort; at 4 years, the OS of all patients in the imatinib cohort was 38%, versus 22% in the preimatinib cohort. However, the rate of alloHSCT was 46% in the imatinib cohort and was 31% in the preimatinib cohort.13 This raises the question of what proportion of the benefit accrued was a direct result of imatinib alone, rather than the contribution made by imatinib to a significantly better initial therapeutic response facilitating more frequent alloHSCT. A Cox multivariate analysis, which took alloHSCT into account, showed only a modest additional benefit with the addition of imatinib (hazard ratio for EFS, 0.64; 95% CI, 0.44 to 0.93; p = 0.02). Importantly, there was significant benefit for OS and RFS. The investigating team, of whom I was a member, concluded that the addition of imatinib to standard therapy considerably improved the CR rate and long-term OS for adults with ALL. However, our data showed that a proportion of the OS benefit derived from imatinib facilitation of alloHSCT. Studies in which the long-term outcome of patients who have been selected by good risk criteria to postpone alloHSCT will eventually inform a more strategic deployment of alloHSCT in this disease. Additionally, non-alloHSCT immunotherapies, such as the bispecific antibody against CD19 and CD3, blinatumomab,35 and chimeric antigen receptor T cells (discussed in the companion article by Sadelain et al), may find a role in postremission therapy of high-risk ALL as a potential alternative to alloHSCT.

UNDER WHAT CIRCUMSTANCES SHOULD WE USE NONMYELOABLATIVE (REDUCED-INTENSITY CONDITIONED) ALLOHSCT?

As an alternative to no transplantation for patients who are beyond the upper age limit for myeloablative alloHSCT or who have comorbidities that rule it out, nonmyeloablative (RIC) alloHSCT is used increasingly widely. Retrospective reports constitute the only evidence base to date, although the United Kingdom National Cancer Research Institute Adult ALL subgroup U.K. ALL14 trial includes a prospective evaluation of RIC alloHSCT. Most published series of RIC include patients beyond CR1, and none confine themselves to Ph+ ALL.

A few key, positive messages regarding RIC alloHSCT in Ph+ ALL emerge from the studies reported to date.47-48 First, RIC can be used, with an acceptable early TRM in patients who are older than those suitable for a myeloablative approach. The median ages reported range from 38 to 50 years, and treatment-related mortality in more recent studies,
which include more patients in CR1, is consistently between 20% and 30%. Currently, no particular conditioning regimen can be considered optimal. Chronic graft-versus-host disease (cGVHD) rates are high, and there is insufficient evidence to determine whether the high rate of GVHD is positively associated with a better disease-related outcome. There likely is scope for approaches in which conditioning regimens that have lower risks of cGVHD are investigated. In summary, nonmyeloablative allogeneic HSCT approaches appear promising and offer DFS rates in Ph+ ALL that, when overtly specified, appear higher than those obtained with chemotherapy and imatinib alone and are in line with what has been achieved by using myeloablative approaches. Two large studies from the IBMTR and EBMT registries reported the comparative outcomes of myeloablative versus RIC alloHSCT in patients with ALL. Ph+ disease was excluded from the IBMTR analysis. The EBMT analysis included 145 patients with Ph+ ALL; among that subgroup, OS was 47% (± 5%) for myeloablative conditioning versus 40% (± 9%) for RIC. In the multivariate analysis of the whole population, the nonrelapse mortality was lower in RIC recipients (hazard ratio, 1.98; p = 0.0001), whereas relapse risk was higher. Multivariate analysis showed that the type of conditioning regimen was not significantly associated with leukemia-free survival. In the IBMTR study, which only included patients with Ph-negative ALL, no independent effect of conditioning intensity was seen. Importantly, all reports of RIC alloHSCT in ALL show poor outcomes when used beyond CR1.

**IS THERE ANY ROLE FOR AUTOLOGOUS STEM CELL TRANSPLANTATION?**

In the largest study of adult ALL ever, U.K. ALL12/E2993, autologous stem cell transplantation (autograft) was compared with chemotherapy in a randomized manner. Chemotherapy was statistically significantly superior. Nonetheless, the concept of high-dose therapy and return of autologous cells continues to be realized under certain circumstances, and studies have reported good outcomes under particular circumstances in which patients are MRD negative at the time of treatment and, usually, continue to receive a TKI. To what extent the autograft contributed to the good outcomes is not clear, because other studies report long-term outcomes in selected patients who are MRD negative and continue to receive TKIs who did not have autografts.

**ADDITIONAL PROGNOSTIC INFORMATION**

Additional genetic information can provide prognostic refinement in Ph+ ALL. High-resolution single nucleotide polymorphism (SNP) arrays identified alterations in the transcription factor gene IKZF1 (IKAROS) essential for lymphoid proliferation and differentiation. IKZF1 deletions, identified in greater than 60% of patients with Ph+ ALL, partly explained the aggressive nature of the disease. At present, these are not actionable genetic lesions. For physicians whose patients are not enrolled in trials and who are struggling with individual alloHSCT decisions, these may be relevant factors in decision making.

**HOW SHOULD TKI BE USED FOLLOWING ALLOHSCT?**

The necessity for TKIs after alloHSCT and the duration, if used, is unknown. When studies have specifically reported, TKIs are described as hard to tolerate immediately after alloHSCT. Only one study has addressed this question directly. The German Multicenter Adult ALL Group carried out a prospective, randomized, multicenter trial that compared the tolerability and efficacy of post-transplantation imatinib administered either prophylactically (26 patients) or only after detection of BCR-ABL1 transcripts (29 patients). The study did not find any difference in outcome between the two arms, but it was noted that, when given prophylactically starting at 3 months after alloHSCT, it was hard to tolerate, and not all patients were able to continue. Early or high-level reappearance of BCR-ABL1 transcripts after alloHSCT identified a small subset of patients who did not benefit from the addition of imatinib. Regular monitoring of BCR-ABL1 transcripts is arguably the most important component of the therapy. Although bone marrow provides a higher sensitivity of detection than blood, it is feasible to monitor blood more regularly. In my personal practice, I do not routinely administer a TKI after alloHSCT in the absence of detectable BCR-ABL transcripts, but I monitor BCR-ABL1 transcripts monthly in peripheral blood and immediately carry out a bone marrow assessment if transcripts are detected.

**WHAT SHOULD BE MONITORED AND HOW CAN IT BE INTERPRETED?**

Monitoring of Ph+ ALL by quantification of BCR-ABL1 transcripts offers a sensitive and specific way of detecting and monitoring disease. The concepts of CMR or MMR, as used in the assessment of patients with CML, often are cited. The clear relevance in CML relates to the internationally standardized therapy, so responses can be compared among patients and among centers. This is far from the case in Ph+ ALL; hence, the level of response and its predictive value are only relevant to the therapeutic scenario in which they have been reported. I urge caution in extrapolating data described in terms of these definitions beyond the original reporting conditions.

**WHAT CAN BE DONE FOR PATIENTS WITH RELAPSED PH+ ALL?**

The outcome of relapsed ALL in adults is poor. Most large studies of relapsed ALL show that factors at diagnosis, such as cytogenetics, do not strongly influence the outcome once relapse has occurred. Time since diagnosis and age are the two strongest predictors of relapse outcome when considering chemotherapy and alloHSCT as therapies. A shorter duration of first remission and older individual age lower the
chance of a good outcome. However, in the TKI era, the mechanisms of resistance are reasonably well studied. At relapse of Ph+ ALL, it is possible now for patients to progress through newer generations of targeted agents in a systematic fashion according to the results of mutational analysis of BCR-ABL1 transcripts. Patients in whom imatinib ceases to produce a response may respond to nilotinib or dasatinib, and there is even an option, ponatinib, for patients with the T315I mutation. Although TKIs are not without adverse effects, and ponatinib in particular carries a risk of cardiovascular events, they are nonetheless a vastly superior option to rounds of myelosuppressive chemotherapy in preserving performance status and being available to and tolerated by patients in the older age range. There is no evidence of long-term survival mediated by TKIs after relapse. Nonetheless, the difference between EFS and OS in relapsed Ph+ ALL is moving apart. Studies should continue to carefully record both, and readers should pay attention. In addition, results with allografts are being reported. Although allografts have uncertain long-term benefits, there are case reports of good outcomes. Immunotherapy without alloHSCT also is an option for the treatment of relapsed ALL. An international, phase II trial of blinatumomab in patients with Ph+ ALL who have experienced relapse after treatment that included a minimum of two lines of TKI therapy has recently been completed, and analysis is underway. Patients with Ph+ ALL can respond to CD19 CART cell therapy.

PH-LIKE ALL

In the so-called Ph-like ALL, t(9;22) is absent, but the leukemia is characterized by a range of genomic alterations that activate a limited number of signaling pathways similar to those activated in Ph+ ALL, some of which may be amenable to inhibition with approved TKIs. The precise definition of these targetable, kinase-activating lesions in clinical practice using standard techniques is not yet clear, but suggested algorithms have emerged that provide practical advice on when and how to consider this subtype of ALL. TKIs have yet to be formally evaluated, except in case reports. Nonetheless, there will be patients in whom physicians wish to consider a TKI as an option, and requests for insurers or health systems to reimburse these agents will have to be taken into account soon.

Disclosures of Potential Conflicts of Interest


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