How I treat Philadelphia chromosome–positive acute lymphoblastic leukemia

Adele K. Fielding
How I treat Philadelphia chromosome–positive acute lymphoblastic leukemia

Adele K. Fielding1

1University College London, Royal Free Campus, London, United Kingdom

The Philadelphia chromosome is present in approximately 20% to 30% of adults with acute lymphoblastic leukemia (ALL). The poor prognosis of this relatively uncommon acute leukemia has led to the rapid adoption of treatment strategies such as unrelated donor hematopoietic stem cell transplant and tyrosine kinase inhibitors into clinical practice, despite a relative paucity of randomized clinical trials. Recently, there has been a surge of interest in the underlying biology of ALL. In combination with an accumulation of more mature clinical study data in Philadelphia-positive ALL, it is increasingly possible to make more rational and informed treatment choices for patients of all ages. In this article, I review available data and indicate how I personally interpret current evidence to make pragmatic treatment choices with my patients, outside of clinical trials. My strongest recommendation is that all physicians who are treating this rare disease actively seek appropriate clinical trials for their patients wherever possible. (Blood. 2010;116(18):3409-3417)

Introduction

Patients with Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL) belong to a readily diagnosable, distinct subgroup comprising 20% to 30% of adults1 and 2% to 3% of children2 with ALL. The Ph chromosome3 is a translocation between the ABL-1 oncogene on the long arm of chromosome 9 and a breakpoint cluster region (BCR) on the long arm of chromosome 22, t(9:22),4 resulting in a fusion gene, BCR-ABL, that encodes an oncogenic protein with constitutively active tyrosine kinase activity. The molecular weight of this protein depends on the precise chromosome breakpoint. Most patients with ALL express a 190-kDa protein (p190) and the remainder a 210-kDa oncoprotein (p210), which is also commonly found in chronic myeloid leukemia (CML).

Although BCR-ABL is the initiator of both Ph+ ALL and CML, numerous differences exist between the diseases both clinically and at a molecular level. Although BCR-ABL may be necessary and sufficient for the development CML, this is not the case for Ph+ ALL. Murine models of CML and Ph+ B-ALL showed that although SRC kinases are not required for the development of CML, they are required for the development of Ph+ ALL.5 In Ph+ ALL, there are many additional epigenetic changes, copy number abnormalities, and mutations downstream of BCR-ABL that contribute to the very aggressive clinical course. Understanding these genetic lesions is progressing rapidly and is relevant both to awareness of the possible limitations of responses to current "targeted" agents for Ph+ ALL and to future, rational design of novel agents.

There is now an accumulation of relatively mature data on the role of tyrosine kinase inhibitors (TKIs) and allogeneic hematopoietic stem cell transplantation (alloHSCT) in the treatment of patients with Ph+ ALL, making it timely to review the treatment of Ph+ ALL. In this discussion, although I refer to insights gained from studies in children, I will confine any specific recommendations for the treatment of Ph+ ALL to adults. My first and overriding recommendation is that patients with Ph+ ALL should be included within clinical trials and consented to appropriate storage and future use of genetic material and cells wherever possible.

How to diagnose Ph+ ALL

Early detection of t(9;22) is now a vital component of the management of ALL. Immediately upon suspicion of the diagnosis of ALL, a bone marrow aspirate and trephine biopsy should be examined by an expert hematopathologist. Blastic transformation of CML should be ruled out by morphologic examination, with the clinician searching for the presence of an underlying myeloproliferative process. Bone marrow—or peripheral blood, if the blast count is high—should be examined by the use of flow cytometry. Specimens from the diagnostic bone marrow aspirate should be sent for both cytogenetic and molecular examination, accompanied by a specific request to seek evidence of the Ph chromosome/BCR-ABL. Cytogenetic examination should comprise examination of metaphases and fluorescence in situ hybridization with probes for BCR-ABL. The presence of additional cytogenetic abnormalities is common and can provide prognostic information. The laboratory providing cytogenetic results should be aware of the therapeutic value of the timely identification of the Ph chromosome. In the case of molecular diagnosis of BCR-ABL, screening for both potential transcripts, p190 and p210, should be undertaken. Where possible, quantitative polymerase chain reaction should be used to document the absolute number of p190 or p210 transcripts, relative to a housekeeping gene.

In addition to the aforementioned suggestions, in my personal practice, I also ensure that a specimen is sent to the ALL molecular minimal residual disease laboratory for the detection of patient-specific immunoglobulin and T-cell receptor rearrangements.6 I also aim, after gaining the patient’s consent, to bank DNA, RNA, and cells wherever there is sufficient material. At diagnosis, I also arrange to tissue-type all patients of a suitable age for bone marrow transplantation, as well as any of their siblings who are willing to be typed. I immediately initiate an unrelated donor search if there are no siblings or where siblings are found not to be human leukocyte antigen matches.
What prognostic factors are known in Ph⁺ ALL?

The presence of the Ph chromosome is, in itself, considered one of the worst prognostic factors in ALL. Standard clinical ALL prognostic factors at diagnosis,⁷,⁸ such as high presenting white cell counts and older age can further adversely affect the outcome of Ph⁺ ALL.⁹ Deletions of chromosome 9p, which are common, worsen the prognosis of t(9;22).¹ The presence of +der(22) is also common, but conflicting data exist on the prognostic relevance. In the UKALLXII/ECOG2993 study, patients with this additional abnormality had a lower risk of relapse on univariate analysis. This finding persisted on multivariate analysis. By contrast, previous studies by Cancer and Leukemia Group B¹⁰ and the Japanese Adult Leukemia Study Group¹¹ found +der(22) to be an adverse prognostic factor. The authors of these studies both included fewer patients than UKALLXII/ECOG2993, and in neither was the finding confirmed by multivariate analysis. In UKALLXII/ECOG2993 high hyperdiploidy (HeH), which is known to confer a good prognosis in ALL when it occurs alone,¹ also was associated with a lower risk of relapse on a univariate analysis. Almost all patients with HeH in that study also had +der(22); therefore, HeH alone was not included in a multivariate analysis.

In addition to gross abnormalities, which can be detected by conventional cytogenetic techniques, small genetic lesions, which can only be detected by high-resolution interrogation of genomic copy number alternations such as single nucleotide polymorphism array screening, are increasingly recognized as having a big impact the prognosis of Ph⁺ ALL. Individual knowledge of such additional genetic lesions is not immediately therapeutically relevant in a routine clinic setting at present because we lack the tools to target them directly and no data are yet available to demonstrate the effectiveness of any specific clinical interventions on the basis of the knowledge of their presence. Despite this, it is important for treating clinicians to be aware of the prognostic relevance of specific genetic lesions, which are sometimes suggested by reports from conventional cytogenetic techniques and are likely to have an impact on therapy in the future. Information on additional genetic lesions in Ph⁺ ALL is given in Table 1.¹²-¹⁶

Treatment of Ph⁺ ALL

Induction therapy for Ph⁺ ALL: Can we define the specific roles of chemotherapy and TKIs?

In the past, induction chemotherapy for Ph⁺ ALL was identical to that used for Ph⁻ disease. Patients with Ph⁺ ALL achieved complete remission (CR) less frequently than their Ph⁻ counter-parts⁷ with CR rates of 60% to 80%. Despite continuing intensive therapy, remission duration was typically short, with a median remission duration of 9 months.¹⁷ Ph⁺ ALL has always been treated on “high-risk arms” of clinical protocols, and it has been assumed that appropriate induction therapy should consist of the most intensive induction regimens available, typically 4-drug regimens involving anthracycline, although this has not been formally tested. As a result of these disappointing clinical outcomes with standard chemotherapy, TKIs were adopted widely into induction therapy protocols for Ph⁺ ALL worldwide, after promising initial studies demonstrating activity in relapsed disease.¹⁸,¹⁹

What have studies taught us about how to use imatinib during the induction of Ph⁺ ALL? Imatinib is the most widely studied drug in this context and has been tested in combination with multiagent chemotherapy in a variety of administration schedules and timings during the initial treatment of Ph⁺ ALL. There has never been a randomized controlled trial in which some patients received imatinib and others received none; hence, the benefits of imatinib in the treatment of Ph⁺ ALL have generally been evaluated by reference to historical control patients. However, the overwhelming weight of evidence suggests that imatinib is safe when given in combination with chemotherapy and helps promote much greater rates of CR. Several studies of imatinib in Ph⁺ ALL have now been completed and published.²⁰-²⁶ Table 1 summarizes the completed studies in which imatinib was used in patients with Ph⁺ ALL and provides induction outcomes, rates of subsequent alloHSCT, where relevant, and overall survival (OS). The table shows that a prominent finding of all the studies is the high CR rate, approximately 95%, with 100% of patients achieving hematologic CR in several studies.

One of the early studies, by the German multicenter ALL group (GMALL), was performed in patients older than 55 years of age and randomized participants to receive imatinib or multiagent chemotherapy for initial induction. In this randomized comparison of the 2 approaches, the overall CR in the imatinib arm was 96%, whereas in the chemotherapy arm it was 50%. Patients in the chemotherapy alone arm were subsequently allowed to receive imatinib; hence, none of the studies in Table 1 include a control arm in which patients never received imatinib. However, in addition to the GMALL study, the excellent responses observed in all the other studies when imatinib is included in induction contrast starkly with the wealth of historical data on poor rates of CR in patients with Ph⁺ ALL and make it impossible to argue against a there being an initial benefit to imatinib when used during induction therapy. A recent, relatively small study from the Northern Italian Leukaemia Group (NILG) has demonstrated a long-term survival advantage to imatinib, with the 59 patients receiving the drug during induction experiencing a significantly greater 5-year OS probability (38% vs...
23%, P = .009) compared to historical controls (N = 35) treated on the same protocol without imatinib.27

All of the studies in younger patients indicate that a greater number of patients than would have been anticipated historically were able to undergo alloHSCT. The transplant rate of the UKALLXII/ECOG2993 Ph+ ALL, preimatinib, who were treated, on a high-risk arm and were all assigned to receive transplant is a good illustration of this point. There was a surprisingly low transplant rate of only 28% of study entrants; many patients unable to receive high-dose therapy and HSCT either did not achieve CR, were too old or unwell to proceed, or else relapsed or died before being able to receive their assigned HSCT.

Can myelosuppressive cytotoxic chemotherapy during induction be reduced or avoided in the imatinib era? The authors of the GRALL (Group Research on Adult Acute Lymphoblastic Leukemia, a French, Belgian, and Swiss collaborative group) study (which has been reported in abstract form to date)28 evaluated imatinib 800 mg per day combined with vincristine and dexamethasone (n = 42), against imatinib 800 mg per day for 14 days combined with hyperCVAD (n = 41). An initial analysis showed that 100% of patients in the imatinib-based treatment group attained CR versus 95% for imatinib-hyperCVAD combination (n = 41). Most patients in this study went on to HSCT, which translated into a 2-year OS of 62%. No significant difference is apparent between the 2 arms now. This study demonstrates that with the addition of imatinib, CR can be achieved in all patients with minimal toxicity; indeed, the addition of multiagent therapy may have added toxicity because induction deaths were found only in the hyperCVAD arm.

These data give a preliminary indication that the almost invariant 5% induction-related mortality for adults with ALL,25 may be avoidable when imatinib is combined with less intensive regimens. Of course, whether this compromises overall treatment efficacy is not known; therefore, the long-term results of this study will be very important. The principle that imatinib may offer good initial responses with less toxicity is also borne out by the imatinib and steroid combination results reported in 30 elderly patients (median age, 69 years) by the Gruppo Italiano (GIEMMA),26 with all achieving hematologic CR with a median survival from diagnosis of 20 months, although continuing drops in the survival curves suggest that there are unlikely to be any long-term disease-free survivors (DFS). Nonetheless, where curative postinduction therapy is unlikely, there is still a great benefit in human terms to a nontoxic therapy that can be given orally.

Limitations of imatinib as an initial therapy for Ph+ ALL.

Despite these promising initial results of imatinib or imatinib and chemotherapy combinations only the small NILG study25 has so far demonstrated long-term survival benefits in patients with Ph+ ALL. As has been reviewed previously, there are theoretical reasons why the benefits of imatinib might be limited. BCR-ABL activity alone is not responsible for the phenotype of Ph+ ALL.5 Imatinib-resistant clones exist, undetectable by direct cDNA sequencing; can be present at diagnosis,80 and bear no relationship to initial CR rate yet predict subsequent poor outcome. Furthermore, acquired resistance to imatinib also occurs. This is most commonly attributable to mutations in the ABL kinase domain, reducing the binding affinity of imatinib and to BCR-ABL amplification. In an M. D. Anderson study, 88% of patients treated with TKIs had detectable mutations at hematologic relapse.31 Hence, without definitive postinduction therapy, the improved initial responses to imatinib are unlikely to translate into improved OS. Theoretically, as described previously, simultaneous inhibition of both tyrosine kinases and SRC kinases holds out more promise of long-term benefit than tyrosine kinase inhibition alone.

What is the present role of dasatinib for induction of Ph+ ALL? Dasatinib is an obvious candidate drug because it possesses a broader spectrum of kinase inhibition activity than imatinib. Phase 2 study data have demonstrated that dasatinib results in 2 to 3 months of complete hematologic responses, which sometimes are accompanied by the disappearance of cytogenetic evidence of t(9;22), in just less than one-half of the patients treated.32 Of pragmatic importance, many preexisting imatinib-resistant mutations did not prevent patients from responding to dasatinib, with the important exception of the T315I mutation.

Results from studies of dasatinib in de novo Ph+ ALL are just beginning to be available. In a recently completed Italian study of outcome to induction therapy only (the data are available in abstract form), 100% of patients with de novo Ph+ ALL who were treated with dasatinib in combination with steroids (but without chemotherapy) achieved CR within 1 month of starting treatment.33 Dasatinib100 mg daily, in combination with hyperCVAD, is also under evaluation in an M. D. Anderson study, and a preliminary report of this phase 2 study has just been published.34 The drug appears tolerable in this combination, although there was some significant nonhematologic toxicity. Interestingly, the CR rate of 94% is less than that observed with the dasatinib and steroid alone combination because of treatment-related mortality (TRM). The estimated 2-year event-free (57%) and OR (64%) of the 35 patients are difficult to evaluate given the small numbers and short follow-up. Molecular responses were observed in this study, but their relationship to outcome is not yet clear.

Central nervous system disease: prophylaxis and treatment.

Imatinib penetrates the central nervous system (CNS) poorly and is suboptimal prophylaxis against recurrence disease in the CNS; therefore, intrathecal prophylaxis must be administered promptly, especially when imatinib is used without multiagent chemotherapy. For patients who have established CNS disease at diagnosis, I treat with standard intrathecal therapy 2 to 3 times per week until the disappearance of blasts, the same as for the treatment of Ph- ALL. Dasatinib achieves better penetration into the CNS than imatinib and has demonstrated activity in patients with Ph+ ALL and CNS disease.35 Although there are fewer mature outcome data, I would consider dasatinib for induction of remission in patients who present with CNS disease. On the basis of available data of dasatinib and chemotherapy combinations, I would combine dasatinib with hyperCVAD if the patient was fit but with steroid alone in older or less fit patients.

Summarizing the data on how to induce remission in Ph+ ALL: personal recommendations.

In my personal practice, despite the lack of evidence from randomized control trials, I am convinced by the overwhelming body of evidence from the aforementioned studies discussed and referenced in Table 220,22-26,32,36 that imatinib-based regimens offer enhanced CR rates and a greater opportunity for patients to proceed to alloHSCT, where appropriate. Hence, I offer an imatinib-based regimen as initial therapy to all patients who present with Ph+ ALL. After discussing the diagnosis, all patients receive a steroid “pre-phase” for 5 to 7 days, during which the genetic and molecular abnormalities can be confirmed and there is time to address fertility issues and consider available clinical trials before starting definitive therapy. For younger, fit patients, I recommend imatinib 600 mg daily (the most commonly studied dose) be added to a standard multiagent chemotherapy induction regimen. Table 1 shows the range of doses used in the various studies of imatinib in patients with Ph+ ALL. My definition of “young” lacks complete precision. Studies of imatinib with standard chemotherapy in patients with Ph+ ALL have usually included patients up to the age of 60 or 65 years but at the same time, studies in
“older” patients with the use of a less aggressive approach have often included subjects ages 55 years and older. Hence, my personal approach is to evaluate all patients between 60 and 65 years as potential candidates for either aggressive or less aggressive approaches depending on prediagnosis performance status, comorbidities, and patient preference. I shall be watching carefully to see how the very high CR rates and lack of significant toxicity of imatinib combined with steroids and minimal chemotherapy turn out with longer follow-up.

For older or less-fit patients, I consider an imatinib- and steroid-alone induction strategy as described by Vignetti et al24 because, in my personal experience, even people of this age who are extremely fit at presentation struggle with the typically intense, myelosuppressive ALL chemotherapy induction regimens. It is not uncommon to find previously fully functional older patients experiencing prolonged hospitalizations and encountering treatment effects that can render them virtually incapacitated and in need of physical rehabilitation at the end of induction. Often, the adverse effects compromise organ function and necessitate reduced dosing and considerable therapeutic delays, which can preclude the planned postinduction therapies. After CR in older patients, I would aim to add chemotherapy to imatinib for a second induction phase but would exercise caution regarding anthracycline and vincristine doses by 50% in patients older than 60 to ensure that all patients receive 4 intrathecal treatments during initial induction. I use intrathecal methotrexate because I am not aware of any convincing data that triple therapy has any substantial benefit over methotrexate alone.

**Postinduction therapy**

**Myeloablative alloHSCT: accepted as the mainstay of postinduction therapy but toxic and not always possible.** Accepted wisdom in the treatment of Ph+ ALL is that all patients should receive allogeneic HSCT as postinduction treatment wherever possible. The potential benefits of alloHSCT in patients with Ph+ ALL have been described in several studies.38-42 For patients who receive HSCT, DFS and OS always appear better than would be expected where treatment is with chemotherapy alone. However, many of the studies of HSCT in patients with Ph+ ALL have considerable selection bias because the authors only report results from patients who have actually undergone transplantation. Laport et al43 reported a 54% 10-year OS for patients who underwent transplantation in first complete remission in the preimatinib era. When investigators consider the transplantation outcome of patients presenting de novo rather than patients who have been referred for HSCT, the potential benefit of alloHSCT to a Ph+ ALL population as a whole, although real, is rather more modest than that suggested by the studies in which the authors only report those who underwent transplantation.

One of the several explanations for the discrepancy in outcomes between transplantation-only studies and studies that include patients from diagnosis is the relative small numbers of newly diagnosed patients with Ph+ ALL who are actually able to undergo transplantation. In UKALL XII/ECOG2993, in which 267 patients with Ph+ ALL were enrolled in the preimatinib era, transplantation was realized in only 28% of the patients. Older age, lack of donor, resistant disease, or relapse before transplant could be performed were the major factors responsible for the low transplant rate in this study. The outcomes for patients receiving allogeneic HSCT (sibling donor, 44% OS at 5 years; unrelated donor, 36% OS at 5 years) appeared vastly superior to those in patients receiving chemotherapy alone, whose survival was only 19% at 5 years. However when the analysis was repeated, removing those patients who had relapsed or died before the median time to alloHSCT or were beyond the upper age limit for transplant, only relapse-free survival remained significantly superior in the transplanted patients. Because of the extensive use of unrelated donors as sources of stem cells in patients without a matched sibling donor, the investigators of UKALL XII/ECOG2993 was unable to demonstrate a donor versus no donor effect—the 5-year OS for those with a sibling donor was nonsignificantly better (34%) than for those without a sibling donor (25%), but many of those without a donor received unrelated donor HSCT. However, authors of the earlier studies have acknowledged that recipients of HSCT had a better prognosis than those receiving chemotherapy alone, and there is some evidence that a “palliative approach” gives as good a survival as a “curative approach.”137 My personal practice is to reduce the anthracycline and vincristine doses by 50% in patients older than 60 to 65 years of age. I ensure that all patients receive 4 intrathecal treatments during initial induction. I use intrathecal methotrexate because I am not aware of any convincing data that triple therapy has any substantial benefit over methotrexate alone.

**Table 2. Studies of imatinib in newly diagnosed Ph+ ALL**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study group</th>
<th>Study name</th>
<th>N</th>
<th>Dose</th>
<th>CR (%)</th>
<th>BMT rate (%)</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomas et al, 200422</td>
<td>MD Anderson</td>
<td>N/A</td>
<td>20</td>
<td>400 mg (600 mg in maintenance)</td>
<td>93</td>
<td>50</td>
<td>75% at 20 mo</td>
</tr>
<tr>
<td>Yanada et al, 200625</td>
<td>JALSG</td>
<td>ALL202Ph+</td>
<td>80</td>
<td>600 mg</td>
<td>96</td>
<td>61</td>
<td>75% at 1 y</td>
</tr>
<tr>
<td>Wassmann et al, 200626</td>
<td>GMALL</td>
<td>N/A</td>
<td>92</td>
<td>400-600 mg</td>
<td>95</td>
<td>77</td>
<td>36% (alternating schedule), 43% (concurrent schedule) at 2 y</td>
</tr>
<tr>
<td>de Labarthe et al, 200727</td>
<td>GRAALL</td>
<td>GRAAPH-2003</td>
<td>45</td>
<td>600 mg</td>
<td>96</td>
<td>48</td>
<td>65% at 18 mo</td>
</tr>
<tr>
<td>Ribera et al, 201028</td>
<td>PETHMA</td>
<td>CSTIBES02</td>
<td>30</td>
<td>400 mg</td>
<td>90</td>
<td>70</td>
<td>30% at 4 y</td>
</tr>
<tr>
<td>Bassan et al, 201029</td>
<td>NILG</td>
<td>09/00</td>
<td>59</td>
<td>600 mg</td>
<td>92</td>
<td>63</td>
<td>38% at 5 y</td>
</tr>
<tr>
<td>Older adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vignetti et al, 200725</td>
<td>GIMEMA</td>
<td>LAL0201-B</td>
<td>30</td>
<td>800 mg</td>
<td>100</td>
<td>N/A</td>
<td>74% at 12 mo</td>
</tr>
<tr>
<td>Ottmann et al, 200726</td>
<td>GMALL</td>
<td>N/A</td>
<td>55</td>
<td>600 mg (imatinib), 50 (chemo)</td>
<td>96</td>
<td>N/A</td>
<td>42% at 24 mo</td>
</tr>
<tr>
<td>Schultz et al, 200930</td>
<td>COG</td>
<td>AALL0031</td>
<td>92</td>
<td>340 mg/m²</td>
<td>Not stated</td>
<td>N/A*</td>
<td>80% (EFS at 3 y)</td>
</tr>
<tr>
<td>Ongoing studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>UK NCRI, ECOG</td>
<td>UKALLXII/ECOG2993</td>
<td>175</td>
<td>600 mg</td>
<td>95</td>
<td>Awaited</td>
<td>Awaited</td>
</tr>
<tr>
<td>N/A</td>
<td>GRAALL</td>
<td>GRAAPH-2COG05</td>
<td>188</td>
<td>800 mg (imatinib DIV), 96 (imatinib hyperCVAD)</td>
<td>100</td>
<td>62</td>
<td>62% at 2 y</td>
</tr>
</tbody>
</table>

Only patients with sibling donors were eligible for transplant. n = 83 evaluable. BMT indicates bone marrow transplantation; CR, complete remission; DIV, High-dose imatinib mesylate combined with vincristine and dexamethasone; EFS, event-free survival; Ph+ ALL, Philadelphia chromosome–positive acute lymphoblastic leukemia; and N/A, not applicable.
LALA94 study were able to show that the existence of sibling donor was independently predictive of a better outcome.

**What if a fully matching donor cannot be found—what is an acceptable donor option?** In those patients in whom a well-matched sibling or unrelated donor cannot be found, the decision whether or not to perform allogeneic HSCT is a very difficult one. Unrelated donors mismatched at 1 or 2 antigens, umbilical cord blood, or haploidentical donors are all potential sources of stem cells. The latter 2 options mean the use of procedure-specific conditioning regimens as opposed to regimens that have been widely evaluated in Ph \(^+\) ALL.\(^{38,39,44}\) Furthermore, it can be difficult to obtain sufficient hematopoietic precursor cells from umbilical cord blood for adult recipients; therefore, this technique usually necessitates a dual cord approach.\(^{45}\) Umbilical cord blood HSCT in adults has a greater TRM than matched unrelated donor HSCT but an equivalent TRM to mismatched unrelated donor stem cells.\(^{46}\)

Haploidentical alloHSCT has been reported to have good results by single centers, but these results rarely have been replicated outside these experienced settings and therefore the procedure typically carries a very high TRM as the result of both graft rejection and severe graft-versus-host disease. A modest series, including 60 cases of ALL, has been reported; only 15 of these cases were Ph\(^+\), and approximately one-half were beyond CR\(^1\). These data have been recently reviewed in detail.\(^{47}\)

**Is reduced-intensity conditioned alloHSCT a good therapeutic option for Ph\(^+\) ALL?** It is clear that there is an upper age limit for the safe administration of myeloablative HSCT in ALL—the TRM can approach 40%, and advancing age is a very important contributing factor to poor treatment-related outcome. Reduced-intensity conditioning may offer an acceptable alternative to myeloablative therapy and has been described in several retrospective series of patients with both Ph\(^+\) and Ph\(^-\) ALL.\(^{48,49}\) Because this approach is a relatively new one to the treatment of ALL, these series include patients beyond CR\(^1\). The largest series to date comprises 97 patients reported to the European Group for Blood and Marrow Transplantation registry who received various different reduced-intensity conditioning regimens, making it impossible to comment on what is the most appropriate regimen. Many received some form of T-cell depletion.\(^{51}\) A 2-year OS of 52% for those transplanted in CR\(^1\) was reported. A recent City of Hope series reported on 24 patients with adults with high-risk ALL treated with fludarabine and melphalan conditioning without T-cell depletion.\(^{52}\) Nearly one-half of the patients were older than 50 years of age, and there was a 2-year OS and DFS of 61.5% with a TRM of 21.5%. This approach is promising but requires careful prospective study required to define its role in Ph\(^+\) ALL. The forthcoming study from the United Kingdom National Cancer Research Institute Adult ALL subgroup, UKALL14, will assign all patients with Ph\(^+\) disease older than 40 years of age to a reduced-intensity conditioned alloHSCT with the use of fludarabine and melphalan but with the addition of alemtuzumab in an attempt to reduce the 86% incidence of graft-versus-host disease that occurred in the City of Hope fludarabine and melphalan series.

**No donor or no wish to transplant? What information is available on continuing consolidation and maintenance chemotherapy in conjunction with TKIs?** If poor donor options are available or transplant is not an acceptable option to the patient, how does the treating physician strike the balance between “pushing” alloHSCT, a treatment with a very high rates of morbidity and mortality, in an era in which the initial promise of targeted therapies may have an impact on the OR, even if alloHSCT is not used?

Continuation of consolidation and maintenance therapy in association with imatinib has not been evaluated as systematically as alloHSCT in patients with Ph\(^+\) ALL because trials to date have generally risk-stratified all younger patients who achieve CR to alloHSCT. Within these studies, the outcome of patients who did not proceed to transplant are very hard to compare with those who have because they are usually older or have comorbid conditions that put them at greater risk of poor outcome. In studies of older patients in whom transplantation has not been performed, there is generally continued a attrition rate,\(^{22,24,53}\) in contrast with the excellent results found in a the population described by Schultz et al\(^{56}\) (upper age 21), where more than 85% were alive and disease free at 3 years without alloHSCT.

For a middle-aged patient who cannot receive HSCT after induction but continues on an imatinib and chemotherapy combination regimen, the likely outcome now lies somewhere in between the poor outcomes in the preimatinib era and the good outcomes found in the children studied by the Children’s Oncology Group (COG). The Japanese Adult Leukemia Study Group ALL202 trial examined the combination of imatinib and chemotherapy in 80 adult patients, 31 of whom did not undergo alloHSCT. Compared with historical control patients (where there were no event-free survivors at 24 months) the 24-month estimated EFS was significantly better for those receiving imatinib as part of their therapy, and there was the appearance of plateau on the Kaplan-Meier curve. However, only 4 patients were at risk at this time point, and it is likely the majority of patients were still on active therapy.

In pediatric practice, there is understandably much more reluctance to use alloHSCT than in adult practice; even fully matched unrelated donor transplantation is not generally recommended for Ph\(^+\) ALL. A recent study of imatinib in 93 children with Ph\(^+\) ALL has further added to the debate as to whether transplantation will eventually become a dispensable part of therapy for Ph\(^+\) ALL. This COG study compared the outcomes of children treated with imatinib containing regimens with historical controls from previous COG studies.\(^{35}\) Imatinib was added to chemotherapy sequentially, in blocks, until the final cohort received imatinib continuously, with all of their chemotherapy courses. The comparison between these patients suggested an enormous survival advantage for the patients treated with imatinib, 3-year EFS of 80%, which was more than twice historical control patients who had a 3-year EFS of 35%, although follow-up was comparably very short for the imatinib study cohort.

Of particular interest to the question of whether or not to transplant, alloHSCT was only permitted on protocol in which a sibling donor was available (although there was a relatively high rate of off-protocol use of unrelated donor alloHSCT), allowing a comparison—by treatment received—of the outcome of group of patients who did (n = 21) and did not (n = 25) proceed to alloHSCT. The outcomes at 3 years were not significantly different between the groups (86% vs 57%), raising for discussion the consideration of whether imatinib/chemotherapy combination might be able to replace alloHSCT for children with Ph\(^+\) ALL. This study is provocative in this interpretation of this result because follow-up is short and the numbers are small, so it by no means answers the question definitively. However, for adults in whom no good donor options are available, the outcome with TKI and chemotherapy combinations may be better than those seen historically with chemotherapy alone, such that a transplant procedure with a very high predicted TRM can now be balanced against a possible better outcome with chemotherapy and TKI combinations.
For those not undergoing alloHSCT, a full course of maintenance therapy is likely to be equally as important as in Ph−-ALL, but there have been no specific studies; hence, an approach to combining TKIs with elements of maintenance therapy cannot be precisely defined. Studies in adults,22,26 have typically used imatinib at 600 mg per day to replace the conventional oral maintenance drugs 6-mercaptopurine and methotrexate and retained the typical maintenance pulses of vincristine and steroid, whereas the investigators of the COG study56 added imatinib to a full schedule of conventional maintenance therapy. Outside a trial, a reasonable approach to maintenance is to give typical ALL maintenance therapy with the addition of daily imatinib but to adjust therapy promptly for lack of tolerance to avoid any periods of no treatment where possible.

Is there a role for autologous HSCT in Ph+ ALL? High-dose chemoradiotherapy and autologous stem cell rescue for ALL has been shown to be inferior to standard consolidation and maintenance chemotherapy in the UKALLXII/ECOG2993 randomized controlled trial for Ph−-ALL.48 Too few autografts (n = 7) were carried out in the Ph+ arm of the study to determine a realistic assessment of their value. However, there are anecdotal reports arising from clinical trials in which small numbers of patients have had good outcomes after autografting in the so-called “imatinib era.” If there is no good allogeneic donor, there are some circumstances in which autografting might be considered for the patient with Ph+ ALL, so long as the patient has achieved a good molecular response. In situations in which therapy duration absolutely needs to be shortened for pragmatic reasons or the patient is intolerant of elements of a standard consolidation or maintenance regimen, autografting this can be a clinical option.

**Personal recommendations for postinduction treatment of Ph+ ALL.** In my personal practice, outside of a clinical trial, I aim to offer alloHSCT to all patients in CR with a suitable donor. I plan the transplant from diagnosis and schedule it for as soon as possible after 2 induction cycles plus imatinib have been completed. If a delay of more than a month is foreseen, I administer another cycle of therapy combined with imatinib. For delays of 2 to 3 weeks, I would continue imatinib and consider adding a cycle of pulsed steroid and vincristine combined with imatinib. For delays of 2 to 3 weeks, I would continue imatinib but to adjust therapy promptly for lack of tolerance to avoid any periods of no treatment where possible.

For donor selection, I would consider, in order of suitability, a matched sibling, a fully matched unrelated donor, and or in some situations a mismatching unrelated donor. I would not generally offer umbilical cord blood or haploidentical transplant to a patient in CR1. However, this begs the question of what care should be offered to a potentially curable patient with Ph+ ALL in whom there is no suitable allogeneic donor. In my own practice, I would not generally offer such a patient a high-risk transplant procedure such as umbilical cord blood or haploidentical transplant unless the patient is at the greatest risk of relapse. This is a situation in which I would take into account the depth of molecular response, the presence of TKI-resistance mutations in BCR-ABL, and even the presence of other poor prognostic factors as discussed previously. If none of the adverse factors is present, I would favor continuing intensive consolidation chemotherapy accompanied by imatinib followed by maintenance therapy plus imatinib rather than a high-risk experimental transplant procedure.

For patients too old or unfit for allogeneic HSCT, I also aim to continue chemotherapy in conjunction with imatinib. However, I am cautious of administering heavy consolidation treatment in older patients, on the basis of both personal experience and the literature. In an early GMALL study in older patients, the toxicity of subsequent consolidation cycles outweighed the benefit particularly in those who have achieved a good molecular response51: patients continued to die both of toxicity and relapse. My personal focus in the older patient is to continue imatinib without interruption in addition to whatever components of a standard maintenance therapy can be tolerated in addition to this. I aim to administer 2 full years of maintenance therapy.

**Can and should imatinib be given after transplantation?**

The authors of several trials have studied the administration of imatinib after transplantation. The recent Programa para el Estudio de la Terapéutica en Hemopatía Maligna study (PETHEMA)55 aimed for all patients to have the drug, but it could only be administered for a median of 3.9 months in 12 of 21 alloHSCTs, and it was interrupted in 10 patients as a result of post-HSCT complications such as graft-versus-host disease. An ongoing GMALL study whose preliminary results were reported in abstract form to date56 randomizes patients after HSCT to either up-front imatinib started at a predetermined time or imatinib started at the time of appearance of BCR-ABL on molecular monitoring. Imatinib is not well tolerated when given early after HSCT. Most patients given imatinib after the detection of BCR-ABL have had a prompt response, and to date, there is no difference between the groups. The authors of a small study from the University of Minnesota showed a trend toward improved outcome in patients who could be treated with imatinib in the pre- and posttransplant period.57 The imatinib arm of UKALLXII/ECOG2993 study has been closed to recruitment. Imatinib appears reasonably tolerable after transplant in this study, but full analyses of these data are awaited.

In my personal practice, outside a trial, I would decide together with the patient, taking into account the patients clinical condition and willingness to undergo repeated bone marrow sampling, whether to monitor BCR-ABL closely on bone marrow samples taken at a minimum of 2 monthly intervals and begin imatinib at first appearance of BCR-ABL or whether to try to give imatinib, regardless.
If and when to stop imatinib

Most trials have continued imatinib per protocol for arbitrarily defined periods after transplant of between 1 and 2 years or for the duration of imatinib maintenance therapy. However, experience leads me to believe that a significant fraction of patients and physician choose to continue the drug when trials have ended, although there are no reports published on this matter. For this reason, I find it hard to make the decision precisely when to stop imatinib therapy in a patient who continues in CR and remains without adverse effect.

What is the role of molecular monitoring of BCR-ABL?

The role of BCR-ABL monitoring in routine clinical practice in Ph+ ALL in the TKI era is not clear. Although it can be comforting in clinical practice when BCR-ABL becomes undetectable, this can lead to a false sense of security in patients with Ph+ ALL. Reports from the preimatinib era suggested a good correlation between BCR-ABL transcript levels and outcome. In the TKI era, BCR-ABL transcript levels have also been correlated with response. However, the long-term outcome in relation to BCR-ABL response to any given therapeutic intervention is hard to interpret. Unlike in CML there is no clear definition of an appropriate BCR-ABL response at a given time during therapy. Lee et al. showed that a 3-log reduction in BCR-ABL transcripts after 1 month of imatinib treatment strongly predicted a reduced relapse risk. By contrast, Yanada et al. observed no association between rapid achievement of BCR-ABL negativity and long-term outcome. The presence of mutations conferring imatinib resistance at diagnosis and their development during therapy may explain why an initial BCR-ABL response might not correlate well with outcome. In my personal practice, I monitor BCR-ABL on bone marrow whenever a patient has a bone marrow examination, but outside of a clinical study I do not oblige patients to have multiple bone marrow aspirations. I use peripheral blood for BCR-ABL monitoring during routine clinical visits. The frequency of monitoring depends on the setting and what the potential therapeutic responses are to what I find. I do not request mutational analysis at diagnosis, as it is unlikely to detect small imatinib resistant clones.

Although monitoring of patient-specific immunoglobulin and T-cell receptor rearrangements is less sensitive than BCR-ABL monitoring, if I am conducting intensive bone marrow monitoring, for example after alloHSCT where intent of therapy is curative and there are several potential interventions to be contemplated, such as immunosuppressant modulation, donor lymphocyte infusions, and the addition or change of TKI, I would usually plan to do both tests at 2 to 3 monthly intervals, if possible, to give the maximum amount of information.

What is the clinical relevance of mutations in ABL that confer resistance to TKIs?

Imatinib inhibits the constitutively active tyrosine kinase function of the BCR-ABL protein product by binding to and stabilizing an inactive, non-ATP binding conformation of the protein. Mutations are most common within the kinase domain of BCR-ABL and can occur within the A (activation)–loop, the P (ATP-binding)–loop region, or at the so-called “gatekeeper” residue threonine 315. Mutations can be primary—that is, present at diagnosis in 40% of patients, although often in small subpopulations and not detectable by conventional sequencing—or can be acquired during treatment. Approximately 80% of patients with Ph+ ALL who relapse during imatinib-based treatment have mutations, commonly in the P-loop region or so-called “gatekeeper” residue, namely, T315I. Dasatinib is active against many (but not all) of the imatinib-resistant mutations, except for the T315I mutation, which confers complete resistance to dasatinib on the basis of both half-maximal inhibitory concentration data and lack of clinical responses. Drugs are in development that may be effective in the setting of the T315I mutation. The criteria upon which to perform BCR-ABL mutation screening clinically are not defined for Ph+ ALL. In patients who are in complete hematologic remission but receiving imatinib therapy, an increase in BCR-ABL level would be an important trigger. After a frank hematologic relapse, it would be important to try and determine to which TKI the patient might be sensitive.

How should we treat relapsed Ph+ ALL?

Once hematologic relapse occurs in adult ALL, subsequent cure is unlikely. Of 609 patients who relapsed after treatment on the UKALLXII/ECOG2293 protocol, only 7% were alive 5 years later. The best outcomes were achieved where alloHSCT was possible. In Ph+ ALL, all patients who are young and fit enough who had a donor will already have undergone alloHSCT, mostly precluding a second transplant. For patients with relapsed disease who have been treated with imatinib already, a phase 2 study indicated that good hematologic responses to dasatinib can be achieved, even in those with imatinib-resistant mutations and that these responses can last some months. However, this is not a curative option and all patients will eventually relapse. My aim where alloHSCT is not possible is to achieve a hematologic response while keeping the patient out of hospital. It is necessary to be frank and open regarding the limitations of therapy. I would prescribe dasatinib with steroid and if the patient could tolerate more chemotherapy, I would add a vinca alkaloid. I would consider adding monoclonal antibodies against CD20.

Authorship

Contribution: A.K.F. wrote the paper.

Conflict-of-interest disclosure: The author declares no competing financial interests.

Correspondence: Adele K. Fielding, University College London, Royal Free Campus, Rowland Hill St, London NW3 2PF, United Kingdom; e-mail: a.fielding@medsch.ucl.ac.uk.


