



# How I treat Philadelphia chromosome–positive acute lymphoblastic leukemia

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**The introduction of agents targeted at specific molecular events is changing the treatment paradigms in a number of malignancies. Historically, we have relied entirely on DNA-interactive, cytotoxic drugs for treating patients with leukemia. Increased understanding of the leukemic cell biology and pathogenesis, and the ways they evade the immune surveillance mechanisms, will likely lead to the development of more effective agents, and regimens less reliant on chemotherapy, able to achieve deep levels of disease eradication. In Philadelphia chromosome–positive acute lymphoblastic leukemia, the introduction of increasingly potent tyrosine kinase inhibitors (TKIs) has revolutionized therapy. These drugs have been established as the cornerstone of any therapeutic strategy in this disease, and a number of trials have better defined the best ways to incorporate them into the established paradigms. Despite using TKIs, we have continued to remain reliant on cytotoxic chemotherapy regimens and allogeneic hematopoietic cell transplant to achieve the best long-term outcomes. However, with the introduction of more potent TKIs and other novel agents, as well as better methods for monitoring minimal/measurable residual disease, we are entering an era where we hope to diminish our reliance on transplantation and cytotoxic chemotherapy in this disease. (*Blood*. 2019;133(2):130-136)**

## Introduction

The pivotal description of the translocation between chromosomes 9 and 22 leading to the short chromosome 22 by Nowell and Hungerford,<sup>1</sup> followed by determination of the translocation product *BCR/ABL1* and its direct role in leukemogenesis eventually led to the development of a number of tyrosine kinase inhibitors (TKIs) that have revolutionized the management of patients with disorders harboring the *BCR/ABL1* transcript.<sup>2-7</sup> In Philadelphia chromosome–positive (Ph<sup>+</sup>) acute lymphoblastic leukemia (ALL), although allogeneic hematopoietic cell transplant (allo-HCT) remains the standard strategy for achieving long-term disease-free survival, increasing number of patients who are unable to undergo the procedure have been treated effectively with regimens combining TKIs with chemotherapy.<sup>8</sup> Fielding and colleagues clearly demonstrated the benefit of the addition of imatinib to standard therapy in these patients.<sup>9</sup> The long-term follow-up of these studies has demonstrated that a number of patients treated with such regimens and without allo-HCT in first remission continue to remain disease-free several years after initiation of therapy raising the probability of achieving cure without allo-HCT (Table 1).<sup>8</sup> However, a significant proportion of patients with this disease continue to fail to achieve long-term cure, with or without allo-HCT (Table 1). The ability to monitor for persistence of residual disease or for molecular recurrence has further opened avenues for deciding who should be transplanted in first remission.<sup>10</sup> Also, the introduction of more potent TKIs and the recent development of effective monoclonal antibodies have provided more options for treating patients with relapsed disease.<sup>11,12</sup> As the number of options for treating patients with Ph<sup>+</sup> ALL have increased, it is

important to select the best potential therapy for each individual patient in order to improve the long-term outcome for all patients. This should take into account the risks and benefits of each strategy, both short term and long term, for each individual. Here, in this case-based review, we discuss how individualized treatment may provide the best outcome for the majority of patients with Ph<sup>+</sup> ALL. Although, based on the author's personal practice, this review focuses on the hyperfractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone (hyper-CVAD) regimen, many of the points illustrated are applicable to other widely used regimens such as the Berlin, Frankfurt, Munster–type regimens.

## Current standard of care in younger patients with no comorbidity

### Patient 1

A 48-year-old man with no significant medical problems presented in March 2011 with fatigue and was found to have a white blood cell count (WBC) of  $153 \times 10^9/L$  with 60% blasts, hemoglobin (Hb) 11.7 g/dL, and platelet count  $26 \times 10^9/L$ . A bone marrow (BM) exam was consistent with the diagnosis of precursor B-cell ALL (CD19<sup>+</sup>, CD20<sup>-</sup>, CD10<sup>+</sup>, CD22<sup>+</sup>, CD34<sup>+</sup>, TdT<sup>+</sup>), and fluorescence in situ hybridization and reverse transcriptase polymerase chain reaction (RT-PCR) were positive for the presence of *BCR/ABL1* (coding for a 210-kDa protein). Cytogenetic analysis showed t(9;22)(q34;q11.2) as well as t(1;6) in 7 metaphases. He was enrolled in the Southwest Oncology Group 0805 (SWOG0805) clinical trial (#NCT00792948) and received initial induction with hyper-CVAD. Dasatinib 100 mg

**Table 1. Selected trials incorporating TKIs in the initial therapy of Ph<sup>+</sup> ALL**

| Reference        | N   | Age, median [range] | Regimen                    | CMR rate, %          | Allo-HCT rate, % | RFS rate, % | OS rate, % |
|------------------|-----|---------------------|----------------------------|----------------------|------------------|-------------|------------|
| <b>Imatinib</b>  |     |                     |                            |                      |                  |             |            |
| 45               | 80  | 48 [15-63]          | Intensive chemotherapy     | 50 (day 63)          | 49               | —           | 76 (1 y)   |
| 39               | 29  | 69 [61-83]          | Corticosteroids            | 4                    | —                | 48 (1 y)    | 74 (1 y)   |
| 46               | 59  | 45 [20-66]          | Intensive chemotherapy     | —                    | 72               | 39 (5 y)    | 38 (5 y)   |
| 9                | 169 | 42 [16-64]          | Intensive chemotherapy     | —                    | 72               | 50 (4 y)    | 38 (4 y)   |
| 57               | 54  | 51 [17-84]          | Intensive chemotherapy     | 45 (overall)         | 30               | 43 (5 y)    | 43 (5 y)   |
| 15               | 133 | 45 [21-59]          | Intensive chemotherapy     | 23 (2 cycles)        | 65               | —           | 46 (5 y)   |
|                  | 135 | 49 [18-59]          | Low-intensity chemotherapy | 29 (2 cycles)        | 62               | —           | 46 (5 y)   |
| 37               | 34  | 45 [24-57]          | Intensive chemotherapy     | —                    | 44               | 46 (5 y)    | 51 (5 y)   |
| 25               | 92  | 10 [1.3-21]         | Intensive chemotherapy     | —                    | —                | 70 (5 y)    | —          |
| <b>Dasatinib</b> |     |                     |                            |                      |                  |             |            |
| 19               | 53  | 54 [24-77]          | Corticosteroids            | 15 (day 85)          | 42               | 22 (20 mo)  | 31 (20 mo) |
| 47               | 72  | 55 [21-80]          | Intensive chemotherapy     | 65 (overall)         | 17               | 44 (5 y)    | 46 (5 y)   |
| 16               | 97  | 44 [20-60]          | Intensive chemotherapy     | —                    | 42               | 62 (3 y)    | 69 (3 y)   |
| 40               | 71  | 69 [55-83]          | Low-intensity chemotherapy | 24 (consolidation)   | 10               | 28 (5 y)    | 36 (5 y)   |
| 26               | 60  | 10.2* [1.5-27.6]    | Intensive chemotherapy     | —                    | 32               | 60† (5 y)   | 86 (5 y)   |
| <b>Nilotinib</b> |     |                     |                            |                      |                  |             |            |
| 31               | 90  | 47 [17-71]          | Intensive chemotherapy     | 77 (3 mo)            | 63               | 72 (2 y)    | 72 (2 y)   |
| <b>Ponatinib</b> |     |                     |                            |                      |                  |             |            |
| 17               | 37  | 51 [27-75]          | Intensive chemotherapy     | 78 (overall)         | 24               | —           | 80 (2 y)   |
| 41               | 44  | 68 [27-85]          | Corticosteroids            | 61 (evaluable; 6 mo) | —                | —           | 87.5 (1 y) |

CMR, complete molecular remission; OS, overall survival; RFS, relapse-free survival.

\*Mean value provided.

†Event-free survival provided.

daily was started on day 1 and was interrupted after 14 days to allow recovery of the blood counts. BM exam on day 21 was consistent with achieving complete remission (CR). BM repeated after 3 months showed CMR. He then underwent an allo-HCT from an HLA-identical sibling with total body irradiation and etoposide as the preparative regimen. There were no major complications, and the patient was started back on dasatinib 100 mg daily ~100 days after the stem cell infusion. This was associated initially with thrombocytopenia leading to the reduction of the dose of dasatinib to 50 mg daily. Later, he developed recurrent pleural effusions (a well-known toxicity of dasatinib<sup>13</sup>) with further reduction of the dasatinib dose to 20 mg daily. He continues to remain in remission for more than 7 years while continuing maintenance low-dose dasatinib.

When an appropriate donor is available and the potential risks of allo-HCT are limited, allo-HCT in first CR remains the standard of care.<sup>14</sup> In the Medical Research Council United Kingdom ALL XII/ Eastern Cooperative Group 2993 trial there was an advantage for patients undergoing allo-HCT in first CR, which was further enhanced when imatinib was introduced after induction.<sup>9,14</sup> This was attributed to be at least in part because of more patients being able to undergo allo-HCT after imatinib was introduced.<sup>9</sup> A number of other studies have suggested a benefit for allo-HCT particularly in younger adult patients.<sup>9,15,16</sup> In the SWOG0805 trial, there was a relapse-free and overall survival benefit for the patients who underwent allo-HCT when a landmark analysis at 175 days posttransplant (the longest time to transplant) was performed.<sup>16</sup> The French group conducted a randomized trial in patients younger

than 60 who received either low-intensity induction with imatinib, vincristine, and steroids or hyper-CVAD plus imatinib.<sup>15</sup> All patients were eligible to undergo an allo-HCT in first CR, and they reported an OS advantage for the patients who received allo-HCT.

Clearly, allo-HCT is a long-established and potent strategy in patients with Ph<sup>+</sup> ALL only limited by its availability and potential risks. The current body of evidence suggests that in younger patients who have a fully matched donor and have no significant comorbid conditions, this strategy continues to be beneficial. Better assays for detecting persistent residual disease that may better identify patients that could be spared the potential toxicity of this strategy are in development. Whether the introduction of more potent TKIs such as ponatinib, able to produce deeper molecular remissions earlier, will have an impact on the role of allo-HCT in Ph<sup>+</sup> ALL will remain to be established.<sup>17</sup> In a younger patient with available donor who is destined to undergo allo-HCT, it can be argued that initial therapy should be limited to TKI plus steroids and vincristine in order to minimize the risks attributable to more intensive chemotherapy.<sup>15</sup> However, a patient unable or unwilling to undergo transplantation likely requires the combination of ALL-based chemotherapy regimens with TKIs.<sup>18,19</sup> Potential benefits of the more intensive regimens including high doses of cytarabine and methotrexate may include deeper disease eradication and better central nervous system (CNS) penetration.

Another area of debate is whether to continue therapy with TKIs after allo-HCT to reduce the risk of relapse.<sup>20</sup> There are limited data in this area, but a number of retrospective analyses have

demonstrated the feasibility of posttransplant maintenance TKI.<sup>20</sup> Small prospective trials, mainly with imatinib, have further suggested that this strategy may be beneficial in reducing the risk of relapse posttransplant.<sup>20</sup> In the only randomized trial conducted to date, engrafted patients received imatinib either prophylactically or after detection of minimal/measurable residual disease (MRD) by RT-PCR.<sup>21</sup> Although there was a trend for longer molecular remission in the prophylactic group, the leukemia-free survival (LFS) and OS were the same in the 2 groups. However, the authors concluded that despite the low rate of compliance in the study, the use of either strategy was beneficial in reducing the risk of hematological relapse and improving long-term outcome.<sup>21</sup> A retrospective analysis by the European Society for Blood and Marrow Transplantation Acute Leukemia Working Party also reported that prophylactic administration of TKIs post-allo-HCT was associated with significant improvement in LFS and OS.<sup>22</sup>

In the author's practice, younger patients with an available donor are encouraged to consider an allo-HCT in first CR especially when the more potent TKI ponatinib is not a component of therapy and when CMR has not been achieved relatively early in the course of therapy. In patients achieving early CMR, a detailed discussion of risks and benefits of allo-HCT vs continued therapy is undertaken to ensure an informed decision process. Several studies have suggested that early initiation of therapy with a TKI,<sup>9</sup> as well as continuous administration of TKI,<sup>23</sup> particularly during consolidation and maintenance (compared with alternating strategies<sup>24</sup>), may improve outcomes. Therefore, with the exception of the first cycle of induction when we administer TKI for only 14 days, we recommend continuous administration of TKI when in CR, based on the experience with TKIs in chronic myelogenous leukemia. We also encourage continuation of TKI therapy post-transplant, when feasible, although there are no extensive published data to support this. Although ponatinib may be the preferred TKI based on its activity against the T315I mutants, there are no data to support the use of any specific TKI over the others, posttransplant.

## Can younger patients without a donor achieve long-term remission without allo-HCT?

### Patient 2

A 23-year-old man was treated for bronchitis with antibiotics without improvement in July 2007. Initial investigations showed a WBC of  $0.2 \times 10^9/L$ , Hb 8.8 g/dL, and platelet count of  $54 \times 10^9/L$ . BM was consistent with precursor B-ALL with the blast cells expressing CD19, CD10, HLA-DR, CD33, TDT, CD34, CD22, and CD79a. Cytogenetics showed the presence of t(9;22)(q34;q11.2), and molecular testing was positive for the *BCR-ABL1* transcripts (coding for a 190-kDa protein). He was started on a clinical trial of hyper-CVAD plus dasatinib (#NCT00390793) and achieved CR after 1 cycle of therapy. He did not have any siblings, and a search to identify an unrelated matched donor was unsuccessful. The patient declined cord blood transplant and completed 7 more cycles of therapy achieving CMR. He received maintenance therapy with dasatinib 100 mg daily with monthly steroids and vincristine. He developed a right-sided pleural effusion after 2 years of dasatinib, which responded to steroids

and reduction of dose to 50 mg daily. He has continued daily dasatinib 50 mg and remained in CR for 11 years.

The investigators from the Children's Oncology Group reported the long-term follow-up of their study in children (median age 10, range 1.3 to 21 years) showing equivalent outcomes in patients who received at least 280 continuous days of imatinib to those who underwent allo-HCT.<sup>23,25</sup> More recently, Slayton and colleagues<sup>26</sup> reported excellent outcomes for 60 children treated with chemotherapy plus dasatinib with 5-year survival of 86%. Of note, only 19 (32%) patients underwent allo-HCT with outcomes similar for those who did and did not undergo allo-HCT. They concluded that allo-HCT should be limited only to patients with high-risk disease based on flow cytometry-based MRD clearance and presence of *IKZF1* deletions at diagnosis.<sup>26</sup> Other studies have also reported on the negative prognostic impact of a number of genomic abnormalities in addition to *IKZF1* deletions, including deletions of *CKND2A/2B* and *PAX5* genes with some maintaining this adverse impact despite allo-HCT.<sup>27-29</sup> These genomic aberrations, as well as other reported prognostic factors such as high presentation WBC or presence of additional cytogenetic abnormalities, are not yet routinely considered when deciding on allo-HCT.<sup>15,30</sup>

Reported pediatric studies have raised questions about the necessity of allo-HCT in first CR. However, the applicability of these data to the adult population remains unproven. Assessment of MRD using RT-PCR for *BCR-ABL1* transcripts after initial induction and consolidation may better allow the identification of patients who are more likely to relapse and therefore should be definitely considered for allo-HCT. Short and colleagues have reported that using the hyper-CVAD regimen plus a TKI (imatinib, dasatinib, or ponatinib) and without allo-HCT, patients who achieve CMR at 3 months had a significantly better survival than those with lesser molecular responses.<sup>10</sup> On multivariate analysis, only achieving CMR at 3 months was prognostic for survival.<sup>10</sup> Others have shown that achieving deeper molecular responses 3 months after achieving morphological CR is associated with better outcomes.<sup>31</sup> Even among the allo-HCT recipients, those who had deeper molecular responses prior to allo-HCT had better long-term outcomes.<sup>31</sup> In a French trial, patients who had achieved CMR seemed to do as well if they did or did not undergo allo-HCT.<sup>15</sup> Furthermore, patients who achieved major molecular response had similar outcomes whether they received allo-HCT or autologous stem cell transplant (SCT).<sup>15</sup> These data suggest that monitoring for MRD using RT-PCR for *BCR-ABL1* transcripts is a very useful tool in assisting management decisions in patients with Ph<sup>+</sup> ALL. This is likely to be even more important if more precise assays for detecting MRD are introduced.<sup>32</sup> North American pediatric trials have commonly used flow cytometry-based assays for detecting MRD.<sup>25,26</sup> However, molecular-based assays such as RT-PCR for *BCR-ABL1* transcripts or clone-specific PCR for immunoglobulin or T-cell receptor gene rearrangements tend to be more sensitive. More recent methods such as amplicon-based next generation sequencing of immunoglobulin/T-cell receptor may overcome some of the limitations of RT-PCR and enhance sensitivity.<sup>33,34</sup> Other novel and highly sensitive assays such as droplet digital PCR are also in development.<sup>35,36</sup> Achieving deep molecular responses using TKI-based regimens has also rekindled interest in autologous SCT with some studies reporting equivalent long-term outcomes for patients undergoing allo-HCT and autologous SCT.<sup>15,37,38</sup> However, this remains a question to be further explored in clinical trials.

## What is the best strategy in elderly and unfit patients?

### Patient 3

A 53-year-old man with morbid obesity, diabetes mellitus, emphysema, and coronary artery disease presented with severe back and chest pain to his local emergency center in August 2004. Investigations ruled out cardiac and other causes, but his blood counts were abnormal including a WBC of  $19.9 \times 10^9/L$ , Hb of 13 g/dL, and platelet count of  $33 \times 10^9/L$ . BM exam was consistent with Ph<sup>+</sup> ALL, and he received induction therapy with hyper-CVAD plus imatinib 400 mg daily on a clinical trial (#NCT00038610). He achieved CR and was referred for allo-HCT. A suitable donor was not identified, and he was considered to be at high risk of developing complications for an investigational transplant. He completed 7 further courses of chemotherapy including 8 intrathecal chemotherapy administrations as devised by the protocol. He remained well and as he had achieved a major molecular response but not CMR, his imatinib dose was increased to 300 mg twice daily during maintenance. He tolerated this well but had diabetes-related renal impairment. Unfortunately, after 8 years in CR, he presented with left eye visual loss, partial ptosis, and decreased hearing in the left ear; magnetic resonance imaging was suggestive of leptomeningeal disease involving several cranial nerves, and examination of cerebrospinal fluid confirmed CNS relapse. BM examination showed molecular relapse. He received intrathecal chemotherapy until his cerebrospinal fluid became negative for leukemic cells as well as systemic therapy with dose-modified hyper-CVAD plus dasatinib for his molecular relapse. His renal function had also deteriorated, and he became debilitated and died of the complications of his concurrent medical conditions.

Treatment of older and medically unfit patients who are unable to tolerate chemotherapy has been difficult. In order to circumvent the toxicity associated with intensive chemotherapy, a number of groups have investigated the use of a TKI with minimal chemotherapy in this population.<sup>19,39,40</sup> Although these studies have produced almost universal responses with no induction mortality, the remissions have not been durable unless consolidated with intensive chemotherapy, autologous HCT, or allo-HCT. The European Working Group for Adult ALL (EWALL) combined dasatinib with vincristine and steroids for the initial therapy of older patients with newly diagnosed Ph<sup>+</sup> ALL, followed by consolidation with more intensive chemotherapy.<sup>40</sup> They reported a CR rate of 96% with a 5-year survival of 36%. Therefore, although reduction or elimination of chemotherapy can reduce the initial morbidity and mortality, long-term cure cannot be achieved in the majority of patients using this strategy. In the same study, EWALL showed that among the patients who relapsed, there was a high incidence of the TKI-resistant T315I mutants.<sup>40</sup> Using more potent TKIs such as ponatinib that are active against resistance-inducing mutations, it may be possible to have higher and more durable responses. However, only limited long-term data with such a strategy are available.<sup>17,41</sup> The choice of TKI in this population should also take into account the presence of concomitant medical disorders and the potential toxicities of various TKIs.

Solitary CNS relapse is uncommon, but with an increasing number of individuals achieving long-term remission, more patients are at risk of developing extramedullary relapse, and appropriate

prophylaxis to reduce this risk is crucial. In the recently reported pediatric study by the Children's Oncology Group, there was a trend toward increased risk of CNS relapse among the non-transplanted patients.<sup>26</sup> Our group has increased the number of intrathecal prophylactic chemotherapy from 8 to 12, and with this strategy, we have decreased this risk significantly in our more recent regimens.<sup>17</sup> Even with allo-HCT, further CNS therapy may be necessary to prevent these events particularly in patients with initial presentation with CNS involvement, although this is not our routine practice.<sup>42</sup>

## What is the role of newer, more potent TKIs?

### Patient 4

A 67-year-old man presented to his local physician in March 2013 with progressive fatigue, fevers, and sinus congestion. A complete blood count showed pancytopenia, and he was referred to a local hematologist who performed a BM exam revealing a hypercellular marrow with 80% cellularity and increased lymphoblasts (47%) with CD34, CD10, TDT, CD19, CD38, CD22, CD52, HLA-DR, and dim CD13 and CD20 expression. PCR was reported as positive for *BCR-ABL1* including both p210 and p190 transcripts. He was enrolled in a clinical trial combining the hyper-CVAD regimen with ponatinib (#NCT01424982)<sup>17</sup> and received ponatinib 45 mg daily, achieving morphological CR as well as CMR after 1 cycle of therapy. His therapy was continued with further cycles of the regimen as well as continuous therapy with ponatinib 45 mg per day. He tolerated ponatinib well, but in November 2013, ponatinib dose was decreased to 15 mg daily after information regarding ponatinib-related cardiovascular risk became available.<sup>43</sup> Alternative TKI therapy was discussed, but the patient chose to remain on the study. He continued to remain in CMR and remained adherent to ponatinib 15 mg daily until in October 2016 when he presented to the emergency center with chest pain. Coronary angiography revealed multivessel coronary artery disease requiring percutaneous balloon dilatation and stent placement. He tolerated the procedure well; ponatinib was discontinued, and he was initiated on maintenance imatinib 400 mg daily, which he continues to receive to date while he remains in CMR.

Despite the revolutionary success of imatinib in the treatment of Ph<sup>+</sup> leukemias, a proportion of patients are resistant to it, and next-generation inhibitors have been developed to overcome this resistance. In Ph<sup>+</sup> ALL, the introduction of imatinib in combination with standard ALL regimens significantly improved long-term outcomes and allowed more patients to undergo allo-HCT in first CR.<sup>9,44-46</sup> However, a significant proportion of patients continue to relapse with 3- to 5-year survival rates of 33% to 46% in the published studies.<sup>8</sup> The introduction of second-generation TKIs capable of overcoming resistance-inducing *ABL1* kinase domain mutations (with the notable exception of T315I) led to their introduction in the management of Ph<sup>+</sup> ALL with a few studies reporting higher progression-free and overall survival, albeit shorter follow-up.<sup>16,31,47</sup>

A number of studies have demonstrated that T315I mutations are commonly detected in patients with Ph<sup>+</sup> ALL who relapse after prior TKI-containing therapy.<sup>19,40,47</sup> In the study by the EWALL, using dasatinib and lower-intensity chemotherapy in older adults, 75% of patients who relapsed and had samples for mutation



analysis had the T315I mutations.<sup>40</sup> Furthermore, using allele-specific oligonucleotide PCR, they demonstrated the presence of the mutants in a number of patients enrolled in the study at the outset and before receiving any therapy.<sup>40</sup> Other studies have also reported the occurrence of *ABL1* kinase domain mutations at relapse.<sup>18,19,47</sup> These data suggest that development of *ABL1* kinase domain mutations, and particularly T315I, is an important contributor to the development of relapse in Ph<sup>+</sup> ALL suggesting that a more potent inhibitor with activity against the resistance-inducing mutations, such as ponatinib, is likely to be beneficial in this disease. Indeed early reports of use of this agent in the frontline setting have suggested impressive activity with high response rates including high and early CMR rates.<sup>17,41</sup> We use ponatinib in the setting of clinical trials in the frontline setting and when possible and in the absence of contraindications in the relapse setting. Chemotherapy-free combination of ponatinib and blinatumomab is under investigation in the frontline therapy, particularly of elderly and unfit patients.

## What are the potential options and outcomes for relapsed disease?

### Patient 5

A 43-year-old man presented to his local doctor in December 2012 with progressive fatigue and was found to have a WBC of  $52.2 \times 10^9/L$  with 79% circulating blasts, Hb of 7.9 g/dL, and platelet count of  $43 \times 10^9/L$ . BM examination revealed 82% blasts consistent with precursor B-ALL, and cytogenetics were positive for the presence of the Philadelphia chromosome with fluorescence in situ hybridization and RT-PCR confirming the presence of the *BCR-ABL1* transcripts (coding for a 190-kDa protein). He was initiated on therapy with the hyper-CVAD plus dasatinib on SWOG0805 protocol (#NCT00792948) and achieved CR after 1 cycle of therapy. He was referred for an allo-HCT, but neither a suitable sibling donor nor a matched unrelated donor could be identified, and the patient declined a haplo-identical transplant. He continued to receive 7 consolidation cycles of chemotherapy with continuous dasatinib 70 mg daily without major complications. He then received maintenance therapy with monthly vincristine and prednisone while continuing dasatinib at 100 mg daily. Maintenance therapy was complicated by cytomegalovirus reactivation requiring therapy with valgancyclovir, as well as episodes of clostridium difficile diarrhea requiring courses of metronidazole and oral vancomycin with good response. He completed 1 year of maintenance followed by dasatinib monotherapy at 100 mg daily until, 5 years later, he was found to have molecular relapse on routine peripheral blood PCR monitoring with a value of 0.21%. A BM examination showed frank morphological relapse with 68% blasts. He received salvage therapy with combination of bosutinib plus inotuzumab and achieved CR, but therapy was discontinued because of suspected veno-occlusive disease of the liver and the detection of a mutant T315I positive clone.<sup>48</sup> He was then initiated on the combination of blinatumomab and ponatinib and after 1 cycle of therapy, achieved a second CMR.<sup>49</sup> He then underwent a double cord blood and natural killer cell allo-HCT with conditioning regimen of lenalidomide, fludarabine, cyclophosphamide, and total body irradiation in January 2018. He has remained well and in CMR with full donor chimerism while continuing posttransplant ponatinib, which was started ~5 months after transplant.

With the development of newer, more potent TKIs, as well as monoclonal antibodies such as blinatumomab<sup>12,50</sup> and inotuzumab,<sup>51</sup> a number of effective salvage options with limited toxicity have become available, thereby allowing the possibility of achieving a second CR before proceeding to allo-HCT. Other strategies such as chimeric antigen receptor T-cell therapy can also be potentially considered in this setting.<sup>52</sup>

## Conclusion

Management of patients with Ph<sup>+</sup> ALL is evolving rapidly. Prior to the introduction of imatinib, few patients survived long-term without undergoing an allogeneic SCT in first CR, and these were typically younger, fit patients.<sup>53</sup> A number of adult and pediatric studies have shown the benefit of the addition of early and continuous therapy with TKIs to the traditional ALL-based regimens.<sup>9,25,26,54,55</sup> In younger, fitter patients and especially using the first- and second-generation TKIs, allo-HCT in first CR remains the standard of care, although long-term data from both pediatric and adult studies suggest the possibility of long-term LFS without an allo-HCT in first CR. Whether the addition of newer, more potent agents such as ponatinib, as well as monitoring for MRD with more reliable and sensitive assays, can change this standard should be evaluated in the setting of carefully designed large randomized trials. In older and unfit patients unable or unwilling to undergo a transplant, use of TKIs in addition to low-intensity chemotherapy does produce high response rates with minimal or no induction mortality.<sup>19,40,41</sup> However, it does not appear that such a strategy can produce long-term RFS, and perhaps future regimens incorporating blinatumomab or inotuzumab may be associated with more durable responses, particularly when combined with the more potent inhibitors. Frontline trials in elderly patient evaluating such strategies are ongoing. Other methods of enhancing the activity of TKIs such as combination with the BCL-2 inhibitor venetoclax have been demonstrated in preclinical studies and may provide a promising approach to be investigated in future trials.<sup>56</sup> The availability of more effective agents both in the frontline and relapse settings is providing a range of possibilities for treating this disease that may allow individualized therapy based on patient characteristics, donor availability (including novel donor sources such as haplo-identical donors), and MRD clearance.

## Authorship

Contribution: F.R. wrote the manuscript.

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## Footnote

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