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Perspective

Adults with Philadelphia Chromosome–Like Acute Lymphoblastic Leukemia: Considerations for Allogeneic Hematopoietic Cell Transplantation in First Complete Remission

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Philadelphia chromosome–like (Ph-like) acute lymphoblastic leukemia (ALL) is a subset of high-risk B cell ALLs. A large proportion of Ph-like ALL cases carry activating kinase mutations that could potentially allow them to be targeted by tyrosine kinase inhibitors. Ph-like ALL is not an uncommon entity, especially among adults, with a frequency exceeding 20%, including in older patients (>60 years old) with ALL. Ph-like ALL is associated with inferior outcomes across all ages, and studies have consistently shown a higher incidence of persistent postinduction minimal residual disease in patients carrying Ph-like ALL compared with other subgroups of ALL, and this translates into inferior leukemia-related outcomes. The inferior outcome of conventional chemotherapy for Ph-like ALL in adults raises the fundamental question of whether all adults with Ph-like ALL require an allogeneic hematopoietic cell transplantation (HCT) in first complete remission (CR1) regardless of other presenting features and treatment response parameters. Here we present and discuss several scenarios in which adults with Ph-like ALL underwent or were considered for HCT in CR1 for various reasons. Although the decision to proceed with HCT was clear and indisputable in some of these situations, in others we struggled with the decision to transplant in CR1 because of the lack of published data regarding the efficacy of allogeneic HCT as consolidation for Ph-like ALL. We emphasize the urgent need for developing well-designed studies to address this important question.

INTRODUCTION

Philadelphia chromosome–like (Ph-like) acute lymphoblastic leukemia (ALL) is a heterogeneous subset of B cell ALLs that shares a similar gene expression profile with Philadelphia chromosome positive (Ph+) ALL but lacks the *BCR-ABL1* translocation [1,2]. A large proportion of Ph-like ALL patients carry activating kinase mutations that could potentially allow them to be targeted by tyrosine kinase inhibitors (TKI) [1,2]. Ph-like ALL can be divided into several genetic subgroups, with the largest group carrying *CRLF2* rearrangement with or without *JAK2* mutation. Other genetic alterations include *JAK2* rearrangements, other *JAK-STAT* mutations, *ABL*-class gene fusions, mutations in other kinases (*FLT3, NTRK3, BLNK,* and *PTK2B*), and *RAS* pathway mutations [1,2]. Ph-like ALL is not an uncommon entity, especially among adults, with a frequency exceeding 20%, including in older patients (>60 years old) with ALL [2,3]. The incidence of Ph-like ALL seems particularly high among Latin Americans [4], and this could be related to an inherited variant in the *GATA3* gene [5].

Ph-like ALL was described originally by 2 independent groups of investigators using microarray analysis to characterize this high-risk gene expression profile entity [6,7]. Although gene expression profiling is the gold standard for diagnosis of Ph-like ALL, the complexity and unavailability of microarray profiling in routine clinical practice precludes its widespread applicability, and therefore various algorithms and methods have been developed to identify ALL cases suggestive for Ph-like expression in a more practical fashion [1,2,8,9]. The variety of proposed methods for diagnosis of Ph-like ALL has contributed to the confusion and lack of consensus with regards to defining this entity as well as comparing the data across different studies. A practical approach to aid diagnosis of Ph-like ALL may be to include sequencing for the common genetic alterations in next-generation sequencing (NGS) panels, as was done in our cases.

Ph-like ALL is associated with inferior outcomes across all ages [1,2,4,6,10]. Studies have consistently shown a higher incidence of persistent postinduction minimal residual disease (MRD) in patients carrying Ph-like ALL compared with other

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subgroups of ALL, and this translates into inferior leukemia-related outcomes overall [1,2,4,6,10]. Among adults, the adverse impact associated with Ph-like ALL has been reported with different adult and pediatric-type chemotherapy regimens [2,4,10]. Nonetheless, it is important to emphasize that Ph-like ALL is a heterogeneous entity that includes diverse genetic subgroups that may not all share the same adverse impact on prognosis, and therefore one particular treatment strategy may not be suitable for all Ph-like ALL. In one study Ph-like ALL patients with *CRLF2* overexpression had inferior remission duration, event-free survival, and overall survival (OS) compared with those with non-*CRLF2* Ph-like ALL despite no significant difference in complete remission (CR) rate or MRD response [4]. The inferior outcome of conventional chemotherapy for Ph-like ALL in adults raises the fundamental question of whether all adults with Ph-like ALL require an allogeneic hematopoietic cell transplantation (HCT) in first CR (CR1) regardless of other presenting features and treatment response. Allogeneic HCT in ALL reduces leukemia relapse compared with chemotherapy alone, and it is routinely recommended for adults with ALL carrying high-risk features if the patient is fit and a suitable donor is available. Today, the difficulty in finding a histocompatible donor for every patient in need of allogeneic HCT is becoming less of an obstacle given the encouraging results of haploidentical HCT in various hematologic malignancies.

Here we present and discuss several scenarios in which adults with Ph-like ALL underwent or were considered for HCT in CR1 for various reasons. Although the decision to proceed with HCT was clear and indisputable in some of these situations, in others we struggled with the decision to transplant or not in CR1 because of the lack of published data supporting the use of allogeneic HCT for Ph-like ALL. Therefore, we have used our clinical experience as well as data from ALL studies in general to make a rational decision on whether to perform allogeneic HCT as consolidation in CR1 for each of the scenarios discussed. We acknowledge that the scenarios presented here are unlikely to cover all indications for allogeneic HCT in Ph-like ALL, but they were chosen to provide examples for scenarios where allogenic HCT is a consideration. We also recognize the short durations of follow-up for these patients after transplantation, and therefore the long-term impact of allogeneic HCT on Ph-like ALL outcomes cannot be inferred from these examples. We emphasize the urgent need for developing well-deigned studies to address this important question.

SCENARIO 1

Persistent MRD after Induction Chemotherapy

S.R. is a 28-year-old Mexican American man diagnosed with B cell ALL with an initial WBC count of 1700/μL. Cytogenetics showed 48,XY,+X,inv(7)(p13q36),+17,add(20)(p13)[2]. NGS revealed the presence of *P2RY8-CRLF2* fusion, consistent with Ph-like ALL. The patient was induced using a pediatric-inspired regimen [11] and had persistent MRD (.043%) by multicolor flow cytometry (MFC) despite 2 cycles of induction. A fully HLA-matched unrelated donor was identified, and he underwent allogeneic HCT after myeloablative conditioning using fractionated total body irradiation in combination with etoposide. He achieved MRD-negative CR post-transplant, but his course was complicated with recurrent gastrointestinal graft-versus-host disease (GVHD) that eventually resolved with steroid therapy. Bone marrow biopsy at 1-year documented continued MRD-negative CR. The patient is now 16 months post-HCT with mild chronic oral GVHD.

Discussion

Consistent with published data, this scenario highlights the finding that Ph-like ALL is a high-risk leukemia, and these patients have a higher tendency to have persistent MRD despite multiple cycles of induction. This high rate of persistent MRD reflects the fact that Ph-like ALL is refractory to conventional chemotherapy, and therefore other approaches, including allogeneic HCT, are required for cure.

The role of allogeneic HCT in this scenario is less debatable given the fact that persistent MRD correlates with shorter remission duration and lower OS in studies of ALL in general, especially in patients who did not undergo alloHCT [12-15]. For adults with ALL who do not achieve MRD response by weeks 8 to 10 from initiating induction, only 10% of them will attain MRD response with continuing chemotherapy by week 16, and this is dependent on ALL risk (0% in high-risk patients) [12]. Allogeneic HCT in CR1 with persistent MRD at week 16 improved OS compared with continuing chemotherapy only (5-year OS, 66% versus 12%; $P < .0001$) [12]. The combination of high-risk genetics (Ph-like ALL) and inadequate response to therapy as well as the availability of fully matched donors in a fit patient prompted our decision to recommend allogeneic HCT in CR1.

SCENARIO 2

Inadequate Therapy Despite Rapid Initial Response

L.S. is a 30-year-old Mexican American man diagnosed with B cell ALL with an initial WBC count of 8800/μL. Cytogenetics showed hyperdiploidy with 53,XY,+X,+5,+18,+19,+21,+21,+22. NGS documented the presence of *CRLF2-IGH* rearrangement. He was induced according to the Children's Oncology Group (COG) AALL1131 regimen; however, his induction course was complicated by asparaginase-induced clinical pancreatitis requiring interruption of therapy. He achieved MRD-negative CR by MFC after first induction; however, further asparaginase was held because of a concern for recurrent pancreatitis [16,17]. He underwent sibling donor allogeneic HCT after fractionated total body irradiation and etoposide conditioning. Post-HCT bone marrow biopsy documented ongoing MRD-negative CR. He is 6 months post-transplant, and immunosuppressive medications are being tapered off.

Discussion

The role of transplant in this scenario is more debatable and controversial. Allogeneic HCT is usually not recommended for early responders if adequate chemotherapy is being delivered and no particular very high-risk genetics are present. Although the patient achieved early MRD response, which reflects a highly chemosensitive leukemia, his treatment course was complicated with asparaginase-induced clinical pancreatitis after just 1 dose of asparaginase, and thus further asparaginase doses were held because of a substantial risk of recurrent pancreatitis [16,17]. Asparaginase is a key drug in ALL therapy and is one of the key components of pediatric-inspired ALL regimens [18]. Studies have shown increased risk of relapse and decreased disease-free survival among patients who receive inadequate doses of asparaginase [19,20].

Our rationale to transplant this patient was based on the inability to deliver curative therapy in the setting of high-risk genetics (Ph-like with *CRLF2-IGH* rearrangement) and the availability of a fully HLA-matched related donor. One could argue that this patient has achieved negative MRD early during treatment, and therefore transplant consolidation is not indicated. However, currently no data exist in adults showing that rapid MRD responders with Ph-like ALL will have similar excellent

long-term outcomes as non–Ph-like ALL early responders, particularly if a key drug like asparaginase has to be omitted early from the regimen. On the contrary, in a small cohort of adults of Ph-like ALL treated with Hyperfractionated Cyclophosphamide, Vincristine, Adriamycin, and Dexamethasone (hyperCVAD), achieving postinduction MRD-negative CR, did not abrogate the adverse impact on median OS (26 months in MRD-negative versus 23 months in MRD-positive, $P = .32$) [4]. Consistent with this finding, MRD status at the end of induction did not impact event-free survival ($P = .67$) or OS ($P = .27$) among pediatric patients (n = 40) with *CRLF2* rearrangement treated on a Children's Oncology Group study [21]. Data on allogeneic HCT are lacking in both reports [4,21]; however, these studies indicate that early MRD response may not overcome the poor prognosis of Ph-like ALL, and this entity may require more aggressive consolidation such as allogeneic HCT regardless of MRD status.

SCENARIO 3

Presence of Other High-Risk Genetics in Combination with Ph-Like Genotype

W.S. is a 48-year-old Mexican American man diagnosed with B cell ALL with an initial WBC count of 28,000/μL and central nervous system involvement. Conventional cytogenetics failed to grow adequate metaphases. Analysis for Ph-like alterations using NGS showed *BCR-ABL1* fusion, *CRLF2-P2RY8* fusion, and extra copies of *IGH* and *RUNX1*. He was treated with a pediatric-inspired regimen along with dasatinib. He achieved CR1 and cleared the cerebrospinal fluid with frequent intrathecal chemotherapy. His sister was identified as a haploidentical matched donor, and he is undergoing preparation for allogeneic HCT using myeloablative conditioning.

Discussion

This scenario illustrates the fact that Ph-like ALL can occur in the context of other cytogenetic abnormalities and mutations, including high-risk alterations [1,2,4,6,22]. Indeed, the co-occurrence of *BCR-ABL1* in association with *CRLF2*-rearrangement in the same leukemia clone was reported recently in a case-series similar to this scenario [22]. Ph+ ALL in adults is a high-risk leukemia, and allogeneic HCT consolidation is indicated in CR1, even in the era of TKI given the survival benefit that has been demonstrated in transplanted patients [23,24].

The decision to transplant this patient was clear in our opinion because of the presence of other high-risk genetics indicating allogeneic HCT in CR1. This could also be applied to other high-risk features, such as *IKZF1* deletion [25], which is frequently encountered in Ph-like ALL cases.

SCENARIO 4

Ph-Like ALL with High-Risk Clinical Features

A.S. is a 70-year-old white man diagnosed with B cell ALL with an initial WBC count of 1 K/μL. Cytogenetics showed normal male karyotype. NGS panel revealed *P2RY8-CRLF2* fusion as well as mutations in *ASXL1, PHF6, U2AF1,* and *ZRSR2*. He was treated with frontline blinatumomab on a clinical trial (NCT02143414) but failed to respond. Subsequently, he received induction therapy with corticosteroid, anthracycline, and vincristine but had refractory disease. He then received reinduction with hyperCVAD and achieved morphologic CR but had MRD at .024% after cycle 1. He achieved MRD-negative CR by MFC after part B hyperCVAD. He then underwent allogeneic HCT from a fully HLA-matched unrelated donor using reduced-intensity conditioning with fludarabine and melphalan. Post-HCT bone marrow examination was consistent with ongoing MRD-negative CR. He developed acute lower gastrointestinal GVHD that resolved with steroid therapy. He is 5 months after transplant.

Discussion

Consistent with prior studies examining the distribution of Ph-like ALL in different age groups, this scenario showed that Ph-like ALL also occurs in elderly patients [2]. This scenario also illustrates the resistance of Ph-like ALL to conventional chemotherapy and immunotherapy. However, the impact of Ph-like genetics on immunotherapy response yet needs to be studied. Although this patient was old, he was fit and had no comorbidities, and given multiple high-risk features including older age, inability to deliver adequate therapy because of age, high-risk genetics, and failure to achieve CR after 2 lines of therapies, we elected to transplant him in CR1. Reduced-intensity conditioning extended the application of allogeneic HCT to older adults with ALL, and it can represent the only curable modality for very high-risk cases [26].

SCENARIO 5

ABL-Class Gene Fusions and the Role of Post-HCT Maintenance Therapy

R.A. is a 26-year-old Mexican American woman diagnosed with B cell ALL with an initial WBC count of 9300/μL. Cytogenetics showed 47,XX,inv(9)(p13q34),+10. NGS revealed the presence of *NUP214-ABL1* fusion, consistent with Ph-like ALL. She was induced with a pediatric-inspired regimen [11], and dasatinib was added during the second cycle of induction after she was found to have persistent leukemia (25% blasts) after induction cycle 1. Bone marrow biopsy at the end of the second cycle showed 3% residual blasts. She underwent sibling donor allogeneic HCT using fractionated total body irradiation and etoposide conditioning. Day 30 post-transplant bone marrow analysis showed persistent MRD at .068% by MFC. She was placed again on single-agent dasatinib 140 mg daily, and bone marrow examination at day 100 showed MRD down to .031%. Six months post-transplant her bone marrow examination showed further reduction in MRD to .015%, and 1-year marrow showed a detectable MRD but at <.01% using MFC. She is now 14 months post-transplant with no evidence of GVHD and remains on dasatinib maintenance.

Discussion

ABL1-class kinase activating alterations including *NUP214-ABL1* represent a subset of Ph-like ALL and occurs in 3% to 12% of cases [1,2,8]. This entity is encountered more frequently in children compared with adults, but it is rarely observed in older adults [1,2]. Ph-like ALL carrying *ABL*-class gene rearrangements (involving *ABL1, ABL2, CSF1R*, or *PDGFRB*) exhibit sensitivity toward TKI therapy (imatinib and dasatinib) in preclinical studies [1,27]. Indeed, there are few reported cases of ALL with *ABL*-activating mutations treated with imatinib or dasatinib alone, but in most cases TKIs were administered in combination with chemotherapy [1,28–30].

Here we illustrate the activity of dasatinib in a patient with Ph-like ALL carrying *NUP214-ABL1* rearrangement when it was given as preemptive therapy after HCT for persistent MRD. Dasatinib therapy achieved clearance of MRD over time in this patient and is an option for this subset of Ph-like ALL. Persistent MRD before and after allogeneic HCT is an adverse predictor for outcomes afterward [31], and novel approaches to integrate along with HCT are warranted to improve outcomes.

The use of maintenance TKI after allogeneic HCT was shown to be feasible in Ph+ ALL patients [32], and in some studies TKI

maintenance has shown favorable outcomes in preventing relapse and improving outcomes in Ph+ ALL [33]. Likewise, this approach can be potentially extended to *ABL1*-class subset of Ph-like ALL who undergo allogeneic HCT.

GENERAL DISCUSSION

The role of allogeneic HCT in adults with Ph-like ALL remains unclear because of a lack of studies specifically addressing allogeneic HCT outcome in this genetic subgroup. Therefore, the decision to proceed to transplant currently is based on the treating physician's judgement as well as extrapolation of data from other ALL studies. The entity is not uncommon and represents a large proportion of adult high-risk ALL cases, particularly in Latinos. Therefore, there is an urgent need to study this entity systemically, preferably through prospective studies where the role of transplant is investigated in the context of MRD response. In addition, the genetic alterations in Ph-like ALL afford an opportunity to intervene with *ABL* and *JAK* inhibitors, and incorporation of these therapies in the context of allogeneic HCT needs to be investigated as well. The major obstacle to systematic studies is no consensus on the diagnostic algorithm for Ph-like ALL; hence, there is heterogeneity in diagnostic criteria among centers. Moreover, making this diagnosis from archived specimens is difficult and limits our ability to perform retrospective studies quickly. Therefore, there is a need to perform well-designed prospective studies through cooperative groups like the Blood and Marrow Transplant Clinical Trials Network using confirmation of diagnosis centrally.

Based on the scenarios we have discussed, one can envision specific clinical situations where the role and timing of allogeneic HCT consolidation needs to be determined by systematic retrospective and prospective studies, as follows:

- *Consolidation with allogeneic HCT based on MRD response.* Persistent MRD during ALL chemotherapy is more common in Ph-like ALL as discussed above. Allogeneic HCT is justified for these cases given the adverse impact of MRD on long-term outcomes in adults with ALL, especially if no HCT is performed. However, given the adverse outcomes of ALL patients who undergo allogeneic HCT with MRD, additional treatments may be necessary before proceeding to HCT. This raises the question on the role of immunotherapy in converting refractory MRD-positive Ph-like ALL cases into MRD-negative cases and whether such therapy will improve HCT outcomes. Blinatumomab has shown an encouraging activity in MRD-positive ALL with a response rate approaching 80% [34]. However, the impact of Ph-like genetic signature on response to blinatumomab and how this could translate into improved survival after allogeneic HCT has not been studied.

The more challenging question is whether we should still recommend allogeneic HCT in CR1 for Ph-like ALL patients with early MRD response and available donor? This question underlines the need to assess the impact of Ph-like genotype as an independent prognostic factor for allogeneic HCT outcome when MRD assessment is integrated in the analysis of initial treatment response.

- *Ph-like ALL who received inadequate initial therapy.* Pediatric-inspired regimens have been safely delivered to younger adults (up to 60 years of age) and have produced better outcomes compared with adult-based regimens, although the 2 approaches have not been compared head-to-head [18]. The specific outcome of Ph-like ALL treated with pediatric-inspired regimens remains unclear, but one can assume that many such cases would have been included in ALL studies, particularly those that include a large number of Latin American patients. However, younger patients treated with suboptimal regimens or situations where key ALL drugs have to be omitted early due to toxicity or when the adult is old (>60 years) where these regimens cannot be delivered safely represent scenarios where patient may not receive adequate initial ALL therapy. For these cases the following question emerges: “will these patients who received inadequate ALL therapy require allogeneic HCT in CR1 if they have Ph-like ALL regardless of their MRD response?” This is an important question, especially in the context of the recent progress in relapsed and/or refractory ALL treatment with the availability of novel effective salvage treatments such as chimeric-antigen receptor T cell therapy, blinatumomab, and inotuzumab when the likelihood of attaining CR2 is better than ever before and therefore provides an opportunity to transplant in CR2 instead. However, the specific activity of these novel therapies in refractory/relapsed Ph-like ALL remains unknown. The decision to defer HCT must be reconciled against the fact that outcomes of HCT in CR2 or beyond is inferior to transplant in CR1 [35].
- *The impact of additional adverse risk factors in Ph-like ALL.* Ph-like ALL can carry other cytogenetic or molecular alterations that can be classified either as favorable or unfavorable findings in ALL. The impact of these findings on prognosis needs to be explored more, as well as how these findings will influence management of Ph-like ALL, especially in the context of recommending early allogeneic HCT.
- *Outcomes after allogeneic HCT in Ph-like ALL.* Studies have shown that allogeneic HCT can overcome pre-HCT conventional high-risk cytogenetics and other clinical features that influence ALL survival when treated with chemotherapy alone [35]. However, for patients with Ph-like ALL who undergo allogeneic HCT consolidation, the question is whether HCT will overcome the poor prognosis of this otherwise high-risk leukemia. Here we need to compare outcomes of Ph-like and non–Ph-like ALL in those who underwent allogeneic HCT in CR1. If the outcomes are different, strategies will have to be developed to optimize pre-HCT therapy as well as post-HCT approaches such as the use of kinase inhibitors to reduce risk of relapse and improve outcomes.
- *The role the maintenance TKI post-transplant.* The prevalence of different activating kinase mutations in Ph-like ALL opens the door for targeted therapy in this entity. The activity of such therapies in Ph-like ALL was demonstrated in preclinical studies and has not been systematically evaluated in clinical trials. Nevertheless, the role of maintenance therapy in Ph-like ALL needs to be studied with regards to its ability to reduce relapse risk and eradicate MRD, especially given the safety profile of these agents (imatinib and dasatinib). Also, if TKI in combination with frontline chemotherapy can overcome the adverse prognosis of Ph-like with chemotherapy, then allogeneic HCT may not needed for these patients. This may also apply to the role of *JAK* inhibitors in the large subset of Ph-like ALL carrying *JAK* mutations or fusions.

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