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Have any strategies in Ph-like ALL been shown to be effective?

Ibrahim Aldoss [a], Anjali S. Advani [b,*]

[a] Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA, USA
[b] Department of Leukemia, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA

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ABSTRACT

Philadelphia-like (Ph-like) acute lymphoblastic leukemia (ALL) is a high-risk subset of B-cell ALL characterized by high rates of treatment failure. Unsatisfactory outcomes with frontline therapy in adults with Ph-like ALL have been observed irrespective of the employed regimen, including modern pediatric-inspired regimens. Notably, Ph-like ALL is not an uncommon entity in adults, and it's prevalence extends to older patients with B-cell ALL. As the majority of Ph-like ALL cases harbor genetic alterations in kinases and/or cytokine receptors, the integration of tyrosine kinase inhibitors in newly diagnosed patients and poor early responders with Ph-like ALL has emerged as an area of active research with several ongoing clinical trials. Furthermore, the encouraging activity of novel therapies such as inotuzumab and blinatumomab in chemo-refractory B-cell ALL has promoted an interest in introducing these agents early in Ph-like ALL management, which may lead to improved cure rates with frontline therapies, sparing more adults from undergoing early allogeneic hematopoietic cell transplantation (HCT). Finally, the high relapse rate in patients with Ph-like ALL, does not necessary correlate with early minimal residual disease (MRD) response, raising the question of consolidation with allogenic HCT in all adults with Ph-like ALL in first complete remission irrespective of MRD response.

1. Introduction

Philadelphia-like (Ph-like) acute lymphoblastic leukemia (ALL) is a relatively newly recognized high-risk subset of B-cell ALL. It's gene expression pattern is similar to Philadelphia-chromosome positive (Ph+) ALL, but in contrast, it lacks the *BCR-ABL1* fusion [1–3]. The majority of Ph-like ALL cases carry recurring genetic alterations that activate kinases or cytokine receptors signaling pathways that are amenable to targeted therapy with small molecules, a key finding supported by preclinical studies [1,2].

The discovery of Ph-like ALL has generated substantial interest, nonetheless, it has also raised challenges in the field [3,4]. First, Ph-like ALL is a common finding in adults with ALL, and it accounts for over 20% of all cases with B-cell ALL, including elderly patients (≥60 years) [2,5]. Intriguingly, the prevalence of Ph-like ALL varies among ethnicities [2,6], and it more frequently affects patients with Hispanic background [7,8]. In a study from MD Anderson Cancer Center (MDACC), over two-thirds of all Hispanic patients with B-cell ALL had the Ph-like genotype [7]. This disparity in the incidence of Ph-like ALL is likely attributed to the distribution of inherited germline polymorphisms among ethnic groups. Polymorphism in the *GATA3* (rs3824662) gene has been linked to the occurrence of Ph-like ALL [9,10], and it is much more prevalent in Hispanics residing in the United States as well as Guatemalans with Native American heritage compared to Europeans [10].

* Corresponding author. Cleveland Clinic Foundation, 10201 Carnegie Ave, Desk CA60, Cleveland, OH, 44195, USA.
E-mail address: advania@ccf.org (A.S. Advani).

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Second, there is no clear consensus with respect to the definition of Ph-like ALL or the diagnostic methodology. While the original definition of Ph-like was established based on microarray gene expression profiling (257- and 110-genes) [1,3], new simplified methods are proposed to allow broader use and rapid diagnosis of Ph-like ALL [11–13]. The topic of Ph-like diagnosis is beyond the scope of this review and readers can be referred to recent excellent reviews addressing this subject in depth [14,15]. Third, Ph-like ALL is not a homogenous leukemia and rather it contains diverse genetic subsets, and each distinct subset is unique in targetable mutations and/or pathways as well as clinical outcomes [7,16]. Thus, not all Ph-like ALLs are the same, and the near future is anticipated to convey a more tailored approach for treating each genetic subgroup.

Finally, Ph-like ALL has poor clinical outcomes even with modern ALL regimens [2,17,18]. This inferior outcome raises many questions related to the desired frontline regimen in Ph-like ALL: (1) the status of incorporating tyrosine kinase inhibitors (TKIs) in ALL regimens, (2) if allogeneic hematopoietic cell transplant (HCT) consolidation is needed for all Ph-like ALL patients, irrespective of early minimal residual disease (MRD) response, and (3) how relapsed/refractory (r/r) Ph-like ALL patients respond to newly approved novel targeted immunotherapies.

1.1. Selection of frontline therapy in adults with Ph-like ALL

Ph-like ALL is correlated with high rates of MRD failure during therapy compared to other B-cell ALL subtypes, translating into a high risk for relapse and low survival [5,7,18,19]. This observation was described in adults with Ph-like ALL irrespective of the selected induction regimen, pediatric-versus adult-based. Table 1 illustrated Ph-like ALL outcomes in adults across studies. A study from MDACC reported a lower rate of MRD clearance in adults with Ph-like ALL compared to Ph + or other B-cell ALL (30% in Ph-like vs. 56% in Ph + vs. 87% in other B-cell ALL, $p < 0.001$). In addition, the study demonstrated a comparable low MRD response in a subset of younger adults (<40 years) with Ph-like ALL treated with either hyperfractionated cyclophosphamide, vincristine, doxorubicin, and

Table 1
Ph-like ALL outcomes in adult studies.

Author & year	Sites	Induction regimens	Setting	n of Ph-like (%)	Median Age (range)	CR rate (%)	MRD- (%)	EFS, RFS, PFS, DOR, DFS	OS	HCT n (%)	Ref
Roberts KG et al. 2017	US multicenter	Variable regimens	ND	194 (20)	21–86	NR	47	5-yr EFS = 23%	5-yr = 24%	7 (4)	2
Jain N et al. 2017	MDACC	HyperCVAD, modified BFM	ND	56 (33)	15–71	89	30	Median EFS = 17.2 months; median DOR = 18.9 months	5-yr = 23%	NR	7
Tasian SK et al. 2017	Multicenter	Variable regimens	ND	18 (20)	43 (19–63)	NR	NR	NR	Median OS = 1.6 months	8 (44)	5
Stock W et al. 2019	US multicenter	C10403	ND	41 (31)	24 (17–39)	NR	NR	3-yr EFS = 42%	3-yr = 63%		19
Chiaretti S et al. 2020	Italian Multicenter	GIMEMA LAL1913	ND	28 (31.8)	18–65	74.1	Week 4 = 22 Week 10 = 47 Week 16 = 58	2-yr EFS = 34% 2-yr DFS = 46%	2-yr = 49%	8 (40)	18
Zhao et al. 2020	COH	Blinatumomab	R/R	23 (55)	35 (18–75)	70	NR	NR	NR	NR	49
Jabbour E et al. 2019	MDACC	Inotuzumab	R/R	12 (23)	36 (20–57)	58	71	1-yr EFS = 33%	1-yr = 33%	6 (50)	52
Aldoss I et al. 2020[a]	COH	Allogeneic HCT	CR1-3	61 (65)	32 (20–70) for CRLF2r, & 37 (18–65) for non-CRLF2r	CR1 = 54 CR2/3 = 46	79	3-yr LFS = 39% for CRLF2r & 50% for non-CRLF2r	3-yr = 55% for CRLF2r & 54% for non-CRLF2r	61 (100)	[a]

n: Number; CR: complete remission, MRD-: negative minimal residual disease; EFS: event-free survival; RFS: relapse-free survival; PFS: progression-free survival; DOR: duration of response; DFS: disease-free survival; OS: overall survival; HCT: Hematopoietic cell transplantation; US: United States; ND: newly diagnosed; NR: not reported; MDACC: MD Anderson Cancer Center; GIMEMA: Gruppo Italiano Malattie EMatologiche dell'Adulto; COH: City of Hope; R/R: relapsed/refractory.

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dexamethasone (hyper CVAD) or a modified Berlin-Frankfurt-Munster (BFM) regimen [7]. Adding a newer generation anti-CD20 antibody, ofatumumab, to the hyper CVAD backbone in adults with $CD20^{+}$ ALL failed to abrogate the low MRD response rate in Ph-like ALL compared to other B-cell ALL [20]. Studies employing pediatric-inspired regimens in young adults with B-cell ALL have also reported poor outcomes for Ph-like disease [18,19]. For example, Ph-like was associated with a lower complete remission (CR) rate (74% vs. 92%) and higher rates of persistent MRD at weeks 4 (78% vs. 41%) and 10 (53% vs. 20%) compared to other B-cell ALL subtypes in the GIMEMA LAL1913 study [18]. In the C10403 regimen (derived from the COG AALL0232) in young adults with newly diagnosed ALL, Ph-like ALL was a predictor of inferior outcomes and high rates of MRD failure [19]. Therefore, current data do not support the administration of one regimen over another for adults with newly diagnosed Ph-like ALL, unlike other B-cell subtypes where pediatric-inspired regimens with adequate asparaginase dosing have shown a survival advantage in young adults [21,22].

Notably, the favorable effect of early MRD clearance in adults with Ph-like ALL is uncertain [7,23], unlike what is established for other B-cell ALL subtypes. This raises the question if post induction therapy should be intensified in all adults with Ph-like ALL irrespective of their early MRD response status. Traditionally, this can be accomplished by either escalating the post induction chemotherapy schedule or consolidating patients with allogenic HCT. In children with Ph-like ALL treated on the Total Therapy XV study, poor early MRD response was successfully overcome with intensifying MRD-based risk directed therapy [24]. In contrary, the ANZCHOF ALL8 study showed a high relapse rate (58%) in children with Ph-like ALL despite utilizing risk-adapted therapy [25]. The clinical benefit of this approach in adults with Ph-like ALL is not defined yet, nonetheless, intensifying conventional chemotherapy in adults with ALL has been a problematic tactic due to increased risk of toxicity, especially in older patients [26,27]. A more appealing strategy in adults with Ph-like ALL is to incorporate novel therapies such as blinatumomab or inotuzumab in frontline regimens, potentially improving efficacy without aggravating toxicity.

We treat our newly diagnosed Ph-negative B-cell ALL patients based on their eligibility for clinical studies. If no study is available, we consider patient age and preexisting comorbidities when selecting the therapeutic regimen. In most cases, the Ph-like status is unavailable at the time we start induction therapy, and thus, the finding of Ph-like status has a negligible influence on the decision of induction choice. While we acknowledge the lack of evidence supporting one particular approach over another, we generally treat our young adults (<40 years) with Ph-like ALL utilizing pediatric-inspired regimens such as the C10403 or a modified BFM, and we attempt to administer adequate doses of asparaginase unless there is a clear contraindication. For older patients with Ph-like ALL, we strongly encourage their enrollment in frontline clinical studies, especially studies that incorporate novel agents, considering their dismal outcomes with conventional chemotherapy in general [28]. If no study is available, we administer a modified adult-based regimen with special emphasis on reducing treatment-related toxicities to allow early introduction of salvage therapy with novel agents. In Ph-like ALL across all ages, we are more inclined to switch from chemotherapy to novel agents sooner rather than later in poor responders or persistent MRD since Ph-like leukemia is typically chemo refractory, and additional chemotherapies unlikely will induce or deepen the remission status.

1.2. The benefit of adding TKI in Ph-like ALL

As mentioned earlier, Ph-like ALL contains diverse genetic alterations which are classified into subgroups. The most prevalent subgroup of Ph-like ALL in adults is the *CRLF2* rearrangement (*CRLF2r*), either with or without *JAK2* mutations, which constitutes over half of all Ph-like ALL cases. Other less frequently defined subgroups of Ph-like ALL include *ABL*-class fusions (~10%), *JAK2*-rearrangements (~7%), other *JAK-STAT* alterations (~7%), *EPOR*-rearrangements (~5%), and *RAS* mutations (~4%) [1,2]. *CRLF2*r is more common in older adults with Ph-like ALL while ABL-class fusions are encountered more in children with Ph-like ALL [1,2]. Notably, not all subtypes of Ph-like have the same devastating clinical prognosis, and cases with *CRLF2r* seem to fare the worst [7]. Despite no difference noted in rates of CR or MRD response among adults with Ph-like ALL who harbor *CRLF2r* or not in one study, the duration of response and survival were inferior in Ph-like with *CRLF2r* compared to non-*CRLF2* Ph-like cases, with a 5-year OS <20% in the former group [7].

Nonetheless, the presence of activated kinase alterations and cytokine receptors in the majority of Ph-like ALL have produced a considerable interest in integrating TKIs in the management of this high-risk leukemia in parallel to the progress that was witnessed in Ph + ALL [29]. Preclinical studies have demonstrated encouraging anti-leukemic activity of TKIs in Ph-like ALL carrying either ABL-class fusions and *JAK-STAT* activating alterations [1,5,30,31]. Furthermore, kinase alterations in Ph-like ALL are potentially leukemogenic and play a key role for initiating and sustaining the leukemia [30], supporting the rationale of targeting these alterations. The encouraging preclinical activity of TKIs in Ph-like ALL has led to the design of several clinical studies incorporating these agents with standard chemotherapy in Ph-like ALL.

Although ABL-class fusions (*ABL1*, *ABL2, CSF1R, LYN, PDGFRA* and *PDGFRB*) account only for the minority of all Ph-like ALL cases, they also respond poorly to chemotherapy. On the other hand, there has been exceptional success in targeting *ABL1* in Ph + ALL [16,32]. In 46 children with ALL and *ABL*-class fusions other than *BCR-ABL1* treated on the AIEOP-BFM protocols, a higher incidence of persistent MRD post induction (71% vs. 19%) and consolidation (51% vs. 5%) were noted in these patients compared to other patients with non-ABL1 fusions treated with the same regimen. For the 13 slow responders with ABL-fusions in which TKIs (imatinib or dasatinib) were added, only one (8%) patient subsequently relapsed in contrast to 8 (24%) relapses among 33 cases who did not receive TKI treatment, and this includes 6 out of 17 patients who had not received alloHCT [32].

Single case reports and case series illustrated encouraging anti-leukemic activity of dasatinib or imatinib in Ph-like ALL with *ABL1*-class fusions, either added to treatment in slow responders, in combination as salvage for relapsed/refractory (r/r) disease or as preemptive maintenance therapy post allogeneic HCT in patients with persistent MRD [1,33–38].

In contrast, the majority of adult Ph-like ALLs have activating JAK-STAT singling pathways due to either *CRLF2*r, *JAK2* fusions,

EPORr, or alterations involving *JAK1*, *JAK3*, *IL7R*, *SH2B3*, *TYK2*, and *IL2RB*. Preclinical studies established the sensitivity of these genetic alterations to ruxolitinib [1,30]. There are a few anecdotal case reports suggesting clinical activity for ruxolitinib in combination with chemotherapy in Ph-like ALL [1,39], however, evidence of single agent activity in this setting is largely missing. The AALL1521 study demonstrated the safety of combining ruxolitinib with chemotherapy in children with B-cell ALL with *CRLF2r* or *JAK* pathway alterations [40]. The phase 2 part of the study is currently enrolling patients using ruxolitinib at a 50 mg/m^2/dose administered for 14 days-on followed by a 14 days-off period (NCT02883049).

There are other ongoing clinical studies combining dasatinib or ruxolitinib with chemotherapy in children and adults with Ph-like ALL (NCT02420717, NCT02723994, NCT03117751, NCT03571321). Table 2 depicted active clinical studies in Ph-like ALL.

Preclinical studies have also demonstrated synergistic anti-leukemic activity when combining mTOR inhibitors with *JAK* inhibitors in Ph-like ALL [41,42]. Moreover, the occurrence of additional recurring activated kinases and cytokine receptors in Ph-like ALL can extend therapeutic treatment in a subset of Ph-like ALL to other TKIs particularly targeting *FLT3*, *TRK*, *MEK* and *FAK* [1,43–45].

At the present time, data is premature to routinely advocate adding TKIs to frontline regimens in adults with Ph-like ALL beyond clinical studies. However, contemplating the safety profile of *ABL1* inhibitors in Ph + ALL and the potential clinical benefit derived from limited retrospective reports [1,32], we suggest adding imatinib or dasatinib to frontline regimens in adults harboring ABL1-class rearrangements is a reasonable approach, particularly if the patient has poor or slow response to induction therapy. In contrast, current evidence doesn't support the practice of combining ruxolitinib in adults with Ph-like ALL and *JAK-STAT* alterations outside clinical trials.

1.3. Novel therapies in r/r Ph-like ALL

While Ph-like ALL is a chemo-resistant disease, interest has emerged in employing novel immune- and targeted therapies. These therapies have produced outstanding activity in r/r B-cell ALL, irrespective of high-risk genetics or leukemia sensitivity toward prior chemotherapies.

Blinatumomab is a CD3/CD19 bispecific antibody that has shown promising activity in r/r Ph-negative B-cell ALL with a CR/CRi rate of 43% [46]. Published studies did not explicitly examine the activity of blinatumomab in Ph-like ALL, however, the response to blinatumomab did not correlate with predictors traditionally conferring resistance to chemotherapy [47,48]. In a case series of 42 consecutive adults with r/r B-cell ALL (≥5% marrow blasts) treated at the City of Hope where archived leukemia genetics were analyzed, 23 (55%) were found to have the Ph-like ALL signature, including 16 with *CRLF2r* and 7 non-*CRLF2r*. The CR/CRi rate was encouraging in individuals with Ph-like ALL (CRLF2r = 75%, non-CRLF2 = 57%), and the response rate was higher compared to patients with other B cell subtypes in this cohort (33%) [49].

Inotuzumab is a CD22 antibody drug-conjugate that has also shown significant activity in patients with r/r B-cell ALL [50], irrespective of their cytogenetic profile [51]. In 12 patients with Ph-like ALL treated at MDACC with inotuzumab, the composite CR was 54%, and response rate was comparable for the Ph-like and non-Ph-like ALL cohorts [52]. In another small cohort from SWOG 1312, a study combining inotuzumab with CVP (cyclophosphamide, vincristine and prednisone) in r/r B-cell ALL, 3 out of 5 patients with Ph-like ALL achieved CR/CRi [53].

Chimeric antigen receptor (CAR) T cell therapy targeting CD19 has produced extraordinary response rates in advanced B-cell ALL across various studies in children and adults [54–58]. Although no study was designed specifically to address the response of CAR T cell therapy in Ph-like ALL, it is likely that many of the enrolled patients with r/r B-cell ALL in CAR T cell studies had Ph-like disease. In a small cohort of 4 children with r/r Ph-like ALL treated with CD19 CAR T cell therapy in the Seattle Children Hospital study, all responded and achieved MRD-negative CR [57].

Table 2
Clinical studies enrolling Ph-like ALL patients.

NCT	Study title	Phase	Sites	Restricted to Ph-like ALL	Age	Actively recruiting
NCT03571321	Ruxolitinib and Chemotherapy in Adolescents and Young Adults With Ph-like Acute Lymphoblastic Leukemia	I	University of Chicago	Yes	18–39	Recruiting
NCT02420717	Ruxolitinib Phosphate or Dasatinib With Chemotherapy in Treating Patients With Relapsed or Refractory Philadelphia Chromosome-Like Acute Lymphoblastic Leukemia	I/II	MDACC	Yes	≥10	Active, not recruiting
NCT02723994	A Phase 2 Study of Ruxolitinib With Chemotherapy in Children With Acute Lymphoblastic Leukemia	I/II	COG	Yes	1–21	Recruiting
NCT03117751	Total Therapy XVII for Newly Diagnosed Patients With Acute Lymphoblastic Leukemia and Lymphoma	II	St. Jude	No	1–18	Recruiting
NCT03020030	Treatment of Newly Diagnosed Acute Lymphoblastic Leukemia in Children and Adolescents	IIII	US multicenter	No	1–21	Recruiting
NCT02883049	Combination Chemotherapy in Treating Young Patients With Newly Diagnosed High-Risk B Acute Lymphoblastic Leukemia and Ph-Like TKI Sensitive Mutations	III	COG	Yes	1–30	Active, not recruiting
NCT03564470	Precision Diagnosis Directing HDACi and TKI Target Therapy for Adult Ph-like ALL	II	Multicenter China	Yes	14–55	Recruiting

MDACC: MD Anderson Cancer Center; COG: Children Oncology Group; US: United States.

Given the favorable activity of these novel therapies in r/r B-cell ALL, the introduction of novel therapies early in the treatment of Ph-like ALL is logical and is an area of mounting investigation. This approach could possibly abrogate the inferior clinical outcomes of Ph-like ALL with frontline regimens, and thus, could spare additional Ph-like ALL adult patients from being allocated to allogeneic HCT consolidation. There are several randomized frontline studies investigating the benefit of adding either inotuzumab (A041501 Alliance study; NCT03150693) or blinatumomab (E1910 study; NCT02003222) in adults with newly diagnosed Ph-negative ALL, and post-hoc subanalysis restricted to Ph-like patients could address to some extent the beneficial effect of early administration of novel therapies in adults with Ph-like ALL.

As these therapies are not yet approved in newly diagnosed ALL, we encourage our Ph-like ALL patients, especially older adults, to be enrolled in frontline studies that include novel therapies. In the absence of studies, we introduce immune- and targeted-therapies early in adults with Ph-like ALL if they show early signs of slow or poor response to induction therapy. For Ph-like ALL patients with early persistent MRD, blinatumomab represents an excellent choice given it's approval in persistent MRD and the encouraging activity in r/r Ph-like ALL [49,59].

1.4. Allogeneic HCT consolidation in Ph-like ALL

Allogeneic HCT is the best-established therapy in preventing leukemia relapse, and it is recommended as a consolidation therapy for adults with high-risk ALL. As Ph-like ALL is associated with a substantial risk of relapse when treated with chemotherapy, the question arises if transplant is warranted in all adults with Ph-like ALL in first CR (CR1), or whether it should be reserved for a selected subset of patients in CR1 [60,61].

Early MRD assessment is a robust prognostic tool to stratify patients with ALL treated with chemotherapy into prognostic subgroups [19,62–64], and a survival advantage is achieved when transplant in CR1 is performed in adults with persistent MRD [62]. While MRD persistence by week 12–16 is a clear indication for transplantation in adults with ALL, the benefit of transplant for early (week 4) persistent MRD that clears eventually by week 12–16 remains debatable. Most patients with Ph-like ALL have persistent MRD during therapy [1,7,18,19], and therefore, the decision to transplant is clear in a large proportion of adults with Ph-like ALL. The GIMEMA LAL1913 study showed that 53% of Ph-like ALL patients were allocated to transplant compared to 20% in non-Ph-like ALL patients when a MRD-oriented approach was commenced [18].

What is less clear is if a transplant is indicated in adults with Ph-like ALL who achieve early MRD response by week 4 or have detectable MRD by week 4 that clears by weeks 12–16. In one adult study, achieving early MRD negativity did not improve the low survival of Ph-like ALL (median OS; MRD- = 26 months vs. MRD+ = 23 months, $p = 0.318$) [17]. Thus, the benefit of early MRD response in adults with Ph-like ALL may not have the same favorable prognosis as other B-cell ALLs, and we could argue that the recommendation for allogeneic HCT in CR1 should be extended to early MRD responders in adults with Ph-like ALL given their unsatisfactory outcomes.

Ph-like ALL can be also manifested by other higher risk features that may or may not correlate with MRD response, including the finding of other high-risk cytogenetics/genetics such as complex karyotype or hypodiploidy. Such features could influence the decision to transplant in Ph-like ALL, regardless of the MRD response status, if the patient is fit and a donor is available. Additionally, not all Ph-like ALLs have the same prognosis, and thus, the recommendation to transplant Ph-like ALL in early MRD responders may differ and could be stratified according to particular genetic alterations, such as *CRLF2r* or *IKZF1* mutation, findings which correlate with inferior outcomes in Ph-like ALL [1,7].

Finally, a key factor that could influence our decision for recommending early transplant in a patient with Ph-like ALL is the inability to deliver adequate curative frontline treatment. This could be the result of either patient age or because the patient developed a toxicity that lead to holding key drugs early during therapy or prolonged periods of therapy interruption. One example is a young adult with Ph-like ALL who develops asparaginase induced pancreatitis during the first or second dose while being treated with a pediatric-inspired regimen, and thus precluding the administration of a key drug in subsequent cycles, and favoring us to recommend consolidation with transplant even if MRD response is achieved early.

While allogenic transplant can overcome high-risk cytogenetics in adults with ALL [65], the success for utilizing allogeneic HCT in Ph-like ALL has not been extensively documented yet. In an unpublished data from City of Hope for 94 adults with Ph-negative B-cell ALL who underwent allogeneic HCT in CR, 61 (65%) patients had Ph-like genetic alterations identified using NGS, including 35 *CRLF2r* and 26 non-*CRLF2r*. The 3-year OS was 55% in patients with Ph-like ALL. The 3-year relapse was higher in *CRLF2r* cases compared to non-*CRLF2r* and other B-ALL ($p = 0.05$). However, we did not find a significant difference in 3-year RFS ($p = 0.74$), OS ($p = 0.88$) or non-relapse mortality ($p = 0.13$) between the 3 subgroups.

Notwithstanding, there are other confounding factors related to the transplant itself which could complicate the decision to transplant based on the risk of relapse and non-relapse mortality, such as the intensity of the conditioning regimen, the type of donor and the utilized graft versus host prophylaxis.

We recommend allogeneic HCT for adults with Ph-like ALL with persistent MRD post consolidation, and we consider transplanting patients with Ph-like ALL who are either early MRD responders or those who clear their MRD by the end of consolidation on an individual basis, depending on age, other high-risk features and ability to tolerate curative chemotherapy regimens. For fit older adults with Ph-like ALL, we routinely consider transplant as a consolidation if a donor is available, irrespective of MRD response, since they are unlikely able to tolerate curative chemo-based therapy.

2. Summary

Ph-like ALL is an unmet medical need in adults with B-cell ALL, and we believe that every patient with Ph-like ALL should be enrolled on clinical study since outcomes with conventional therapies are largely unsatisfactory. Additional research is warranted to optimize frontline approaches to improve Ph-like ALL patient's survival, and this will likely be accomplished by integrating TKIs and novel agents early in the treatment of Ph-like ALL patients, and identify a reliable algorithm to assign high risk patients for an early allogeneic HCT consolidation.

Disclosure of conflicts of interest

IA serves on an advisory board with Amgen, Kite Pharmaceuticals, Jazz, AbbVie and Agios, he is a consultant for Autolus Therapeutics, and research support from MacroGenics and AbbVie. ASA has received research support and honoraria/grant support from Pfizer, research support from Abbvie and Amgen, and honoraria from Kite Pharmaceuticals.

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