Seminars in Hematology 57 (2020) 137–141

Contents lists available at ScienceDirect

Seminars in Hematology

journal homepage: www.elsevier.com/locate/seminhematol

Review

Philadelphia chromosome positive acute lymphoblastic leukemia in adults: Therapeutic options and dilemmas in 2020

Lori Muffly[a,*], Partow Kebriaei[b]

[a] Division of Blood and Marrow Transplantation, Stanford University, Stanford CA
[b] Department of Stem Cell Transplantation and Cellular Therapy, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

ARTICLE INFO

Keywords:
Acute lymphoblastic leukemia
Transplantation

ABSTRACT

The incorporation of tyrosine kinase inhibitors (TKI) into front-line therapy for adults with Philadelphia chromosome positive acute lymphoblastic leukemia has dramatically altered response rates and significantly improved outcomes, such that this entity may no longer be considered a high risk acute lymphoblastic leukemia subgroup. In this review article, we summarize approaches to front-line therapy in the TKI era, including intensive chemotherapy-based regimens and deintensified therapy. We also review optimal disease monitoring strategies, discuss the role of consolidative hematopoietic cell transplantation, and touch on options for relapsed disease. The incorporation of novel targeted agents in conjunction with TKIs into front-line therapy will likely alter the future therapeutic approaches to this disease.

Introduction

Prior to the advent of tyrosine kinase inhibitors (TKIs), the prognosis for adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) was generally dismal. For example, data from the largest prospective clinical trial in adult ALL conducted in the pre-TKI era, UKALLXII/ECOG2993 which enrolled from 1993 to 2004, demonstrated a 5-year overall survival (OS) of 22% for Ph+ ALL, and confirmed that consolidation with allogeneic hematopoietic cell transplantation (HCT) significantly improved outcomes for appropriate patients [1]. Subsequently, the UKALLXII/ECOG2993 trial opened a cohort testing the incorporation of imatinib into front-line therapy for Ph+ patients and found that the addition of imatinib significantly improved OS from 22% to 38% [2].

Over the last decade further dramatic progress has occurred on several fronts in this disease. Second and third generation TKIs have been incorporated into a variety of therapeutic backbones with encouraging results. A deeper understanding of molecular risk variants that co-exist with *BCR-ABL1* and advances in assays to monitor for measurable residual disease (MRD) and kinase resistance mutations have further personalized the approach to Ph+ ALL. HCT, once available only to younger patients with sibling donors may now be performed successfully across the age spectrum using a variety of donors and stem cell sources. Finally, highly active targeted immunotherapies, currently available in the United States for patients with relapsed/refractory disease, are quickly moving into front-line trials for adults with Ph+ and Ph-negative ALL.

With this success and array of therapeutic options brings a variety of dilemmas for the practicing clinician and Ph+ ALL patient. In the current article, we will review the existing data and evidence to help guide front-line therapy options, discuss optimal monitoring strategies, examine the role of HCT in the modern era, and touch on treatment options for relapsed/refractory disease.

Front line therapy: Choice of TKI to combine with intensive chemotherapy

Results from a variety of studies incorporating imatinib into front-line intensive chemotherapy regimens for adults with Ph+ ALL demonstrated that the addition of imatinib increased response rates and improved OS relative to historical controls that were treated without TKIs [2-7]. However, the depth of response and relapse-free survival (RFS) even after the addition of imatinib left room for improvement. For example, although the overall CR rate was 92% in the cohort of patients treated with imatinib and chemotherapy on the UKALLXII/ECOG2993 trial, the 4-year RFS was 50%, and dropped to 18% in patients who did not receive consolidative HCT [2]. Similarly, in a long-term follow-up report from the MD Anderson Cancer Center (MDACC), the CR rate following imatinib plus hyperCVAD (cyclophosphamide, vincristine, Adriamycin,

* Corresponding author. Lori Muffly MD, MS, Division of Blood and Marrow Transplantation, Stanford University, 300 Pasteur Drive H0144, Stanford, CA 94305
E-mail address: lmuffly@stanford.edu (L. Muffly).

https://doi.org/10.1053/j.seminhematol.2020.09.002
0037-1963/

and dexamethasone) was 93%, but the rate of complete molecular response (CMR; defined as absence of detectable *BCR-ABL1* transcripts by RT-PCR) by real-time quantitative polymerase chain reaction (RT-PCR) was only 45%, and the estimated 5-year disease-free survival (DFS) was 43% for patients who achieved CR [3].

The desire to deepen remissions and improve survival resulted in trials of second and third generation TKIs incorporated into front-line chemotherapy for adults with Ph+ ALL. Dasatinib has been evaluated both in combination with intensive chemotherapy and with chemotherapy-light/free regimens (reviewed in next section). Among 72 patients (median age 55 years) treated with dasatinib plus hyperCVAD on a Phase II trial at MDACC, 96% attained CR following the first cycle, with 65% achieving CMR at some point in the course of therapy and only 12 patients proceeding onto consolidative HCT [8]. However, the median 5-year DFS was only 44% with 13 relapses (7 with T315I mutations), 20 deaths in CR1 (7 post-HCT, 3 during induction, 10 after induction), and toxicity leading to dasatinib discontinuation in 12 patients, of which 6 were due to pleural effusion. The authors amended the protocol midway to reduce the dasatinib dose to 100 mg daily for the first 14 days followed by 70 mg continuously beginning with the second cycle. In another Phase II study evaluating dasatinib plus hyperCVAD conducted by the United States Intergroup (SWOG0805) including patients up to age 60, the CR rate was 88% (MRD rate unknown), and 3-year RFS for patients who achieved CR was 62% with 69% 3-year OS. This trial differed from the MDACC report in that it was a younger patient cohort and over half of the patients underwent allo HCT in CR1 [9]. Nilotinib has also been tested in combination with intensive chemotherapy. The Korean Society of Hematology reported results of a Phase II trial of nilotinib with multiagent chemotherapy, demonstrating a 91% CR rate (overall CMR 86%), with 2-year RFS and 2-year OS of 72% [10].

Finally, the use of ponatinib as front-line therapy has been evaluated in combination with hyperCVAD. In a single institution report from MDACC on 76 patients (median age 47 years), ponatinib (final dosing schema amended to 45mg for the first 14 days followed by 30 mg daily from cycle 2 until CMR, then 15 mg daily through maintenance) was combined with hyper-CVAD and resulted in a 100% CR rate (83% CMR), estimated 3-year EFS and OS of 70% and 76%, respectively, with a median of 36 months of follow-up [11]. Importantly, patients with clinically significant cardiovascular disease were excluded from the trial, yet hypertension developed in 50%, significant thrombotic events in 13%, 21% developed pancreatitis, and 37% of patients required ponatinib dose reductions. An update of this data recently presented in abstract form [12]. With a median follow-up of 44 months, the 3-year and 5-year EFS were an estimated 78% and 74% and the 3-year and 5-year OS were an estimated 71% and 68%.

There have been no published or reported studies prospectively comparing the results of different TKIs with chemotherapy as upfront therapy for adults with Ph+ ALL, although in children dasatinib was shown to be superior to imatinib [13]. Thus, the choice of TKI is currently based on the institutional protocol available, patient comorbidities and TKI tolerability, consolidation options (see HCT section below), and TKI availability/insurance coverage. For patients in which a chemotherapy-based regimen is considered, we generally recommend the use of a second or third generation TKI given the evidence that these agents can induce deeper remission and most reports demonstrate favorable survival outcomes relative to outcomes reported with first generation TKIs. Finally, appropriate CNS prophylaxis with a minimum of 8 to 12 intrathecal therapies is critically important for all adults with Ph+ ALL, regardless of front-line regimen or TKI administered.

Front-line therapy: Evidence for deintensifying the regimen

The significant activity of second and third generation TKIs in Ph+ ALL led several study groups to challenge the notion of whether intensive chemotherapy is still required to effectively treat Ph+ ALL in adults. To test this hypothesis, the European Group for Research on Adult ALL Ph+ conducted a randomized study evaluating imatinib plus low dose chemotherapy versus imatinib plus hyperCVAD with HCT consolidation for appropriate patients treated on either study arm. The overall 5-year EFS and OS for the entire study cohort was a disappointing 37.1% and 45.6%, respectively, with no significant differences in outcomes between the two study arms. The European Working Group on Adult ALL then conducted a study in adults 55 and older (median age, 69 years) of dasatinib in combination with low-dose chemotherapy induction and consolidation; only 7 patients received HCT [14]. Although nearly all patients achieved CR, the relapse rate was similarly high at 54% and the vast majority of relapses were associated with the T315I mutation. The 5-year RFS and OS were 28% and 36%, respectively.

The results of at least 3 studies of chemotherapy-free induction regimens in adult Ph+ ALL have been presented in abstract form [15-17]. The Phase II US Intergroup 10701 trial tested dasatinib plus dexamethasone induction/intensification followed by a central nervous system (CNS) prophylaxis block and reduced intensity conditioning based HCT consolidation [15]. With median follow-up of just under 2 years, In 65 evaluable patients, 86% achieved CR, and 23 deaths had occurred. In the phase II Italian GIMEMA LAL1811 study for patients aged 60 and older, ponatinib 45 mg daily plus steroids resulted in a 90% CR (45% CMR) rate [17] However, dose reductions were common and 26 serious adverse events were reported, of which 13 were related to ponatinib. Finally, the Italian GIMEMA group recently presented early results of the LAL2116 D-ALBA study evaluating blinatumomab plus dasatinib as a chemotherapy-free front-line regimen [16]. In this preliminary report of 63 patients, the overall CMR rate was 55.6% and only 6 relapses had occurred, but follow-up was limited to just over 1 year.

Thus, although data is accumulating for d-intensification of front-line chemotherapy, there remains no clear consensus on the optimal approach in adults. As we await maturation of the deintensification studies, we currently recommend that younger patients or those with few comorbidities and preserved functional status receive an intensive chemotherapy-based regimen with a second or third generation TKI. In older patients or those whom are otherwise not candidates for more intensive chemotherapy, we recommend a TKI plus deintensified chemotherapy or a TKI-steroid approach. The duration of TKI maintenance following front-line therapy has not been well studied in adults; we therefore, recommend ongoing/indefinite TKI maintenance, as tolerated, in patients who do not undergo HCT. Relapses have been commonly reported in patients receiving reduced deintensified front-line regimens, including CNS relapses, and treating clinicians who take this approach must be sure to administer adequate CNS prophylaxis. Additionally, assessment of the risks and benefits of HCT as remission consolidation should be performed for the individual patient. As discussed in greater detail below, accumulating retrospective data suggests that MRD response may be used to determine consolidation strategy in adults with Ph+ ALL; specifically, that patients achieving MRD negative CMR after intensive induction and TKI therapy may have durable remission without the need for upfront allogeneic HCT. However, MRD driven consolidation (HCT vs no HCT) has not been prospectively tested in adult Ph+ ALL.

Strategies for disease monitoring

The routine assessment of MRD response to therapy is standard of care for ALL in both children and adults. A variety of different methodologies for MRD measurement have been studied, and are available to practicing clinicians, yet little definitive evidence exists to support the superiority of one method over another [19,20]. There is general consensus, however, that any assay must be validated, reproducible, and sensitive to at least the 10^{-4} level in order to be considered appropriate for MRD detection in ALL [21,22]. In the United States, MRD in adults with Ph+ ALL is commonly assessed via quantification of *BCR-ABL1* transcripts by RT-PCR, as validated PCR assays are readily available, sensitive, and ongoing monitoring using this technique may be performed using peripheral blood in an approach similar to that used in chronic myeloid leukemia [23].

There is a growing evidence that achievement of MRD negativity 1 to 3 months after beginning second or third generation TKI-containing therapeutic regimens is associated with superior outcome, and that rising MRD later in the disease course typically heralds fulminant relapse [14,18,24]. For example, among adults treated with hyper-CVAD+TKI containing regimens who did not undergo allogeneic HCT at MDACC, achievement of CMR at 3 months following initiation of therapy was highly associated with superior RFS and OS, more so than MRD response at time of morphological CR [18]. Similarly, ample data exists that MRD response prior to HCT predicts post-HCT relapse, and that emergence of MRD following HCT highly suggests pending relapse [25-27]. Further, MRD results are currently actionable with MRD-guided interventions and risk adapted consolidation.

In addition to MRD monitoring, evaluation for TKI resistance mutations is essential in patients with primary refractory disease, rising MRD, or overt relapse. In particular, the T315I mutation, which confers resistance to all first and second generation TKIs, has been identified in over half of patients relapsing after dasatinib based front-like regimens [8,14]. Finally, the detection of additional cytogenetic abnormalities, particularly involving the loss of chromosome 9/9p, as well as certain genomic mutations involving *IKZF1* have been shown to result in poor outcomes [28,29] Conventional cytogenetics should be assessed at diagnosis and relapse, and consideration for mutational analysis by next generation sequencing should be considered at the same time points as detection of high-risk mutations may aid in prognostication and guiding postremission decision making.

The role of HCT for consolidation

Consolidation with allogeneic HCT in CR1 is still considered the standard of care for patients with a suitable human leukocyte antigen donor receiving upfront therapy with a first or second generation TKI, largely based on date from two prospective multicenter trials. In the SWOG0805 intergroup study, patients up to age 60 years received up to 8 cycles of alternating hyperCVAD with high dose cytarabine and methotrexate plus dasatinib [9]. Patients with a matched sibling or unrelated donor received consolidation with a uniform, total body irradiation-based, myeloablative HCT in CR1 followed by dasatinib maintenance up to 5 years; patients without a donor received maintenance with vincristine and prednisone for 2 years and dasatinib indefinitely. Eighty-eight percent of patients reached CR or CR with incomplete count recovery, and 42% percent underwent transplantation. With a median follow-up of 36 months (range, 9-63), OS and RFS were 69% and 62%, respectively, at 3-years for the whole population. The 12-month OS and RFS for the transplanted group were 87% and 71%, respectively. Notably, landmark analysis at 175 days from CR showed a significant benefit for OS and RFS in the transplanted group, P= .037 and .038, respectively [9]. However, the conclusions from this study were limited by the lack of MRD information on the patients.

In the prospective study conducted by the French cooperative group, Group for Research on Adult Acute Lymphoblastic Leukemia, 2 different schedules of imatinib-containing induction were investigated with the primary objective of identifying the rate of major molecular response after 2 cycles of therapy, and enabling more patients to proceed to transplant [30]. Patients were offered an allogeneic HCT if they had a matched donor, or autologous HCT if they attained a major molecular response and no donor. Overall, 77% of patients were able to proceed to transplant; 63% allogeneic, 14% autologous. With a median follow-up of 4.8 years, the 5-year EFS and OS rates were estimated at 37.1 and 45.6%, respectively [30]. Allogeneic HCT was associated with a significant benefit in RFS (hazard ratio [HR] 0.69, P= .036) and OS (HR 0.64, P= .02). However, notably, patients who achieved a complete molecular response at the end of 2 cycles of therapy did not benefit from RFS (HR 1.02, P= .96). Furthermore, in patients achieving a major molecular response, the outcome was similar after autologous and allogeneic HCT [30].

These findings from the Group for Research on Adult Acute Lymphoblastic Leukemia study underscore the importance of MRD as a tool to help inform the decision to proceed to HCT and suggest that patients who are MRD negative after induction therapy may not need HCT for consolidation. This observation is very relevant for patients who are treated with third generation TKIs such as ponatinib which result in very high complete molecular response rates [11]. Thus, the recommendation to proceed to transplant in first CR in MRD negative patients is less clear. In the absence of a prospective clinical trial, we recommend an individualized discussion with the patient weighing the expectation of durable first remission with their current therapy versus the expected survival following transplant taking into account factors that will significantly impact transplant outcomes, such as the patient's performance status, comorbidities, and donor availability.

The benefit to TKI maintenance following transplant has been extrapolated from largely retrospective studies [31-35] and very small prospective studies [35-38] without adequate statistical power. Nevertheless, the observations in sum suggest benefit for TKI maintenance [39]. The largest retrospective report was from the European Blood and Marrow Transplant (EBMT) registry, in which the Acute Leukemia Working party[8] analyzed the outcomes of 473 allo-HCT Ph+ ALL patients who were transplanted in CR1 and received post HCT TKI maintenance (n = 157). The post-allo-HCT use of TKI was associated with improved OS (HR = 0.44, P= .002), DFS (HR = 0.42, P= .004) as well as reduced rate of relapse (HR = 0.4, P= .01) [34]. In the largest prospective, randomized study by the German Multicenter study group for adult ALL (GMALL), 55 patients with Ph+ ALL were randomly assigned to receive imatinib as prophylaxis (n = 26) or pre-emptive therapy based on MRD positivity (n = 29) following allogeneic HCT in CR1 or CR2 for one year [36]. The majority of patients were transplanted in CR1 in both groups, and other key transplant factors were similar between the 2 groups. Following HCT, patients in the prophylactic and pre-emptive arms were initiated on imatinib at a median of 48 days (range 23-88 days) and 70 days (range 39-567 days), respectively. Imatinib was stopped prematurely in approximately 2/3 of both groups both groups with median duration of imatinib 245 days for the prophylactic group and 191 days for the pre-emptive group. The 5-year OS rates were excellent in both the prophylactic and pre-emptive groups at 80% and 75%, respectively. Although the rate of molecular recurrence was significantly lower in the prophylactic group, 40% versus 69%, P= .046, the rates of event-free and OS did not differ between the 2 groups, suggesting that pre-emptive therapy was adequate in preventing overt relapse [40].

Based on these observations both EBMT [41] and the American Society for Transplantation and Cellular Therapy [42] recommend that all patients with Ph+ ALL should be offered TKI maintenance following transplant either in a prophylactic or pre-emptive manner with frequent MRD monitoring in the peripheral blood and less frequently in the bone marrow. The recommendation for which TKI to use, and the duration of maintenance is less clear. The EBMT guidelines suggest starting with imatinib unless there is evidence for resistance with persistent MRD, or if there was a history of CNS involvement since imatinib does not penetrate into the CNS; in these cases they recommend using dasatinib that has CNS penetration [41]. However, increasing data support the superiority of newer generation TKI, and thus if a patient is receiving newer generation TKI, the authors would recommend continuing the current TKI post transplant; if persistent MRD, then changing to another TKI. Finally, there is very little data on the optimal duration of TKI maintenance with studies reporting intended durations of 1 [36] to 5 years[9]. In an effort to study this question, data for 165 patients with Ph+ ALL who consecutively underwent a first allogeneic HCT in complete remission at MDACC from 2001 to 2018 were retrospectively reviewed (Saini, Blood, in press). TKI maintenance was administered to 59% of patients, either in a prophylactic (n = 71) or pre-emptive manner (n = 26) with significant benefit noted in progression-free survival (PFS). In an effort to evaluate the impact of maintenance duration, patients who were alive in CMR at 3 months post HCT and still taking TKI (n = 84) were studied. The median duration of TKI maintenance was 13 months (range 0.23-74 months), with median duration between stopping TKI and last follow-up 20 months (range 0.23-161 months). On a competing risk regression model, patients who continued TKI maintenance had a significantly lower rate of relapse (HR 0.12, P= .045) compared to patients who stopped before 2 years. Among patients who took TKI for more than 2 years, there was only one relapse (Saini, Blood, in press).

Treatment options for relapsed disease

Approval of effective salvage therapies in B-lineage ALL has changed the treatment landscape for patients with relapsed disease, resulting in more patients achieving remission, and subsequently proceeding to transplant with a possibility for cure [43]. Blinatumomab, a bispecific T-cell enagager targeting CD19 was evaluated in the phase II ALCANTARA trial for patients with relapsed-refractory Ph+ ALL [44]. The findings from this study were similar to the confirmatory blinatumomab study for Ph-negative B-ALL [45], with 36% overall survival (ORR) after 2 cycles of treatment, and 44% of patients proceeding to SCT [46]. Blinatumomab in combination with ponatinib was studied in 20 patients with Ph+ ALL resulting in a 65% ORR and median survival of 14 months [47]. Inotuzumab ozogamicin (IO) is an immune-conjugate comprised of an anti-CD22 antibody linked to calicheamicin. In a phase III trial of IO administered as first or second salvage for relapsed-refractory ALL, IO resulted in significantly better ORR (88% vs. 32%, P< .0001), median survival (7.7 vs. 6.7 months, HR 0.77, P= .02), and 2-year survival rate (23% vs. 10%) compared to best standard of care; Ph+ patients comprised 13% of IO patients and 17% of the SOC group [46]. IO was combined with bosutinib in 16 patients with relapsed-refractory Ph+ ALL [48]. The combination was safe, and resulted in an ORR of 81% (CMR 55%). Among 13 responding patients, 6 proceeded to allogeneic HCT, with 5 remaining alive and in remission at last follow-up [48]. Finally, immunotherapy in the form of chimeric antigen receptor (CAR) modified autologous T cells (CAR T) result in very high and deep response rates; data from the global ELIANA trial for pediatric and young adult patients with relapsed-refractory ALL (n = 75, 37% high-risk karyotype including Ph+) showed an ORR of 68%, notably all response MRD negative [49]. Subsequent CAR trials, including studies in adults have shown similarly favorable CR rates [50,51]. However, approximately 50% of responding patients subsequently relapse [49-51], underscoring the need for determining predictors of relapse following CAR therapy in efforts to determine which patients may benefit from further therapy [52].

Conclusion

In conclusion, the adoption of TKI into the treatment schedule of patients with Ph+ ALL has led to significant improvement in OS, such that the long-standing classification of high-risk for this subset of ALL patients is now debatable. Furthermore, refinements in molecular techniques to monitor for disease response and evaluate for resistance to therapy allows for more precise delivery of therapy, and therefore overall better outcomes. For younger and fit patients we recommend an intensive chemotherapy-based regimen with a second or third generation TKI, given the preponderance of data supporting that these newer TKI induce deeper remission. In patients who are not candidates for more intensive chemotherapy, we recommend TKI plus de-intensified chemotherapy or a TKI-steroid approach. Consolidation with transplant should still be considered the standard of care for patients receiving first or second generation TKI but may be debated in patients who achieve MRD negativity with a third generation TKI, such as ponatinib. Finally, all patients with Ph+ ALL should be offered TKI maintenance following transplant either in a prophylactic or pre-emptive manner for a duration of at least 2 years.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Fielding AK, Rowe JM, Richards SM, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALLXII/ECOG2993. Blood 2009;113(19):4489–96.
[2] Fielding AK, Rowe JM, Buck G, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. Blood 2014;123(6):843–50.
[3] Daver N, Thomas D, Ravandi F, et al. Final report of a phase II study of imatinib mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Haematologica 2015;100(5):653–61.
[4] Yanada M, Takeuchi J, Sugiura I, et al. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group. J Clin Oncol 2006;24(3):460–6.
[5] Bassan R, Rossi G, Pogliani EM, et al. Chemotherapy-phased imatinib pulses improve long-term outcome of adult patients with Philadelphia chromosome–positive acute lymphoblastic leukemia: Northern Italy Leukemia Group protocol 09/00. J Clin Oncol 2010;28(22):3644–52.
[6] Vignetti M, Fazi P, Cimino G, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. Blood 2007;109(9):3676–8.
[7] Hatta Y, Mizuta S, Matsuo K, et al. Final analysis of the JALSG Ph+ALL202 study: tyrosine kinase inhibitor-combined chemotherapy for Ph+ALL. Ann Hematol 2018;97(9):1535–45.
[8] Ravandi F, O'Brien SM, Cortes JE, et al. Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer 2015;121(23):4158–64.
[9] Ravandi F, Othus M, O'Brien SM, et al. US intergroup study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Philadelphia chromosome positive ALL. Blood Adv 2016;1(3):250–9.
[10] Kim DY, Joo YD, Lim SN, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Blood 2015;126(6):746–56.

[11] Jabbour E, Short NJ, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study. Lancet Haematol 2018;5(12):e618–ee27.
[12] Short NJ, Kantarjian H, Ravandi F, Huang X, Daver N, DiNardo C. Long-term safety and efficacy of hyper-CVAD plus ponatinib as frontline therapy for adults with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. Blood 2019;134(supplement 1):283.
[13] Shen S, Chen X, Cai J, et al. Effect of Dasatinib vs Imatinib in the Treatment of Pediatric Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA Oncol 2020;6(3):358–66. doi:10.1001/jamaoncol.2019.5868.
[14] Rousselot P, Coude MM, Gokbuget N, et al. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. Blood 2016;128(6):774–82.
[15] Wieduwilt MJ, Yin J, Wetzler M, et al. A Phase II study of dasatinib and dexamethasone as primary therapy followed by hematopoietic cell transplantation for adults with Philadelphia chromosome-positive acute lymphoblastic leukemia: CALGB Study 10701 (Alliance). Blood 2016;128(22):2782.
[16] Chiaretti S, Bassan R, V A, Elia L, et al. Dasatinib-blinatumomab combination for the front-line treatment of adult PH+ ALL patients. Updated results of the GIMEMA LAL2116 D-ALBA trial; on behalf of GIMEMA acute leukemia working party. Blood 2019;134(Supplement_1):740.
[17] Martinelli G, Piciocchi A, Papayannidis C. e. First report of the Gimema LAL1811 phase II prospective study of the combination of steroids with ponatinib as frontline therapy of elderly or unfit patients with Philadelphia chromosome–positive acute lymphoblastic leukemia. Blood 2017;130(suppl 1):99.
[18] Short NJ, Jabbour E, Sasaki K, et al. Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2016;128(4):504–7.
[19] Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta–analysis. JAMA Oncol 2017;3(7):e170580.
[20] Wood B, Wu D, Crossley B, et al. Measurable residual disease detection by high-throughput sequencing improves risk stratification for pediatric B-ALL. Blood 2018;131(12):1350–9.
[21] van Dongen JJ, van der Velden VH, Bruggemann M, Orfao A. Minimal residual disease diagnostics in acute lymphoblastic leukemia: need for sensitive, fast, and standardized technologies. Blood 2015;125(26):3996–4009.
[22] Short NJ, Jabbour E, Albitar M, et al. Recommendations for the assessment and management of measurable residual disease in adults with acute lymphoblastic leukemia: a consensus of North American experts. Am J Hematol 2019;94(2):257–65.
[23] Radich J, Yeung C, Wu D. New approaches to molecular monitoring in CML (and other diseases). Blood 2019;134(19):1578–84.
[24] Yoon JH, Yhim HY, Kwak JY, et al. Minimal residual disease-based effect and long-term outcome of first-line dasatinib combined with chemotherapy for adult Philadelphia chromosome-positive acute lymphoblastic leukemia. Ann Oncol 2016;27(6):1081–8.
[25] Bader P, Salzmann-Manrique E, Balduzzi A, et al. More precisely defining risk peri-HCT in pediatric ALL: pre- vs post-MRD measures, serial positivity, and risk modeling. Blood Adv 2019;3(21):3393–405.
[26] Logan AC, Vashi N, Faham M, et al. Immunoglobulin and T cell receptor gene high-throughput sequencing quantifies minimal residual disease in acute lymphoblastic leukemia and predicts post-transplantation relapse and survival. Biol Blood Marrow Transplant 2014;20(9):1307–13.
[27] Pavlu J, Labopin M, Niittyvuopio R, et al. Measurable residual disease at myeloablative allogeneic transplantation in adults with acute lymphoblastic leukemia: a retrospective registry study on 2780 patients from the acute leukemia working party of the EBMT. J Hematol Oncol 2019;12(1):108.
[28] Short NJ, Kantarjian HM, Sasaki K, et al. Poor outcomes associated with +der(22)t(9;22) and -9/9p in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia receiving chemotherapy plus a tyrosine kinase inhibitor. Am J Hematol 2017;92(3):238–43.
[29] Fedullo AL, Messina M, Elia L, et al. Prognostic implications of additional genomic lesions in adult Philadelphia chromosome-positive acute lymphoblastic leukemia. Haematologica 2019;104(2):312–18.
[30] Chalandon Y, Thomas X, Hayette S, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood 2015;125(24):3711–19.
[31] Akahoshi Y, Nishiwaki S, Mizuta S, et al. Tyrosine kinase inhibitor prophylaxis after transplant for Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer Science 2019;110(10):3255–66.
[32] Nishiwaki S, Miyamura K, Kato C, et al. Impact of post-transplant imatinib administration on Philadelphia chromosome-positive acute lymphoblastic leukaemia. Anticancer Res 2010;30(6):2415–18.
[33] Kebriaei P, Saliba R, Rondon G, et al. Long-term follow-up of allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: impact of tyrosine kinase inhibitors on treatment outcomes. Biol Blood Marrow Transplant 2012;18(4):584–92.
[34] Brissot E, Labopin M, Beckers MM, Socié G, Rambaldi A, Volin L, et al. Tyrosine kinase inhibitors improve long-term outcome of allogeneic hematopoietic stem cell transplantation for adult patients with philadelphia chromosome positive acute lymphoblastic leukemia. Haematologica 2015;100(3):392–9.
[35] Chen H, Liu K-y, Xu L-p, et al. Administration of imatinib after allogeneic hematopoietic stem cell transplantation may improve disease-free survival for patients with Philadelphia chromosome-positive acute lymphobla stic leukemia. J Hematol Oncol 2012;5(1):29.
[36] Pfeifer H, Wassmann B, Bethge W, et al. Randomized comparison of prophylactic and minimal residual disease-triggered imatinib after allogeneic stem cell transplantation for BCR-ABL1-positive acute lymphoblastic leukemia. Leukemia 2013;27:1254–62.
[37] Wassmann B, Pfeifer H, Stadler M, et al. Early molecular response to posttransplantation imatinib determines outcome in MRD+ Philadelphia-positive acute lymphoblastic leukemia (Ph + ALL). Blood 2005;106(2):458–63.
[38] Ribera JM, Oriol A, Gonzalez M, et al. Concurrent intensive chemotherapy and imatinib before and after stem cell transplantation in newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Final results of the CSTIBES02 trial. Haematologica 2010;95(1):87–95.
[39] Warraich Z, Tenneti P, Thai T, et al. Relapse prevention with tyrosine kinase inhibitors after allogeneic transplantation for Ph+ ALL, a systematic review. Biol Blood Marrow Transplant 2020;26(3):e55–64. Epub 2019 Sep 23. doi:10.1016/j.bbmt.2019.09.022.
[40] Ottmann OG, Pfeifer H. Management of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Hematol Am Soc Hematol Educ Prog 2009:371–81.
[41] Giebel S, Czyz A, Ottmann O, et al. Use of tyrosine kinase inhibitors to prevent relapse after allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: A position statement of the acute leukemia working party of the European society for blood and marrow transplantation. John Wiley and Sons Inc.; 2016. p. 2941–51.
[42] DeFilipp Z, Advani AS, Bachanova V, et al. Hematopoietic cell transplantation in the treatment of adult acute lymphoblastic leukemia: updated 2019 evidence-based review from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant 2019;25(11):2113–23. Epub 2019 Aug 22. doi:10.1016/j.bbmt.2019.08.014.
[43] Jabbour E, Short NJ, Jorgensen JL, et al. Differential impact of minimal residual disease negativity according to the salvage status in patients with relapsed/refractory B-cell acute lymphoblastic leukemia. Cancer 2017;123(2):294–302.
[44] Martinelli G, Boissel N, Chevallier P, et al. Complete hematologic and molecular response in adult patients with relapsed/refractory Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia following treatment with blinatumomab: results from a phase II, single-arm, multicenter study. J Clin Oncol 2017;35(16):1795–802.
[45] Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol 2015;16(1):57–66.
[46] Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. New Engl J Med 2016;375(8):740–53.
[47] Assi R, Kantarjian H, Short NJ, et al. Safety and efficacy of blinatumomab in combination with a tyrosine kinase inhibitor for the treatment of relapsed Philadelphia chromosome-positive leukemia. Clin Lymph Myel Leuk 2017;17(12):897–901.
[48] Jain N, Cortes JE, Ravandi F, et al. Inotuzumab ozogamicin in combination with bosutinib for patients with relapsed or refractory Ph+ ALL or CML in lymphoid blast phase. Blood 2017;130(Supplement 1):143.
[49] Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. New Engl J Med 2018;378(5):439–48.
[50] Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. New Engl J Med 2018;378(5):449–59.
[51] Turtle CJ, Hanafi L-A, Berger C, et al. CD19 CAR–T cells of defined CD4+: CD8+ composition in adult B cell ALL patients. J Clin Invest 2016;126(6):2123–38.
[52] Hay KA, Gauthier J, Hirayama AV. Factors associated with durable EFS in adult B-cell ALL patients achieving MRD-negative CR after CD19 CAR T-cell therapy. Blood. J Am Soc Hematol 2019;133(15):1652–63.