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Current Approaches to Philadelphia Chromosome–Positive B-Cell Lineage Acute Lymphoblastic Leukemia: Role of Tyrosine Kinase Inhibitor and Stem Cell Transplant

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Abstract

Purpose of Review Over the past two decades, tyrosine kinase inhibitors (TKIs) have changed the management of patients with Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL), and this has led to significant improvement in their outcome. In this review, we will provide an overview of the current understanding of treatment of Ph+ ALL focusing on TKIs, alloHSCT, and novel therapies.

Recent findings The advent of more potent TKIs and the novel therapeutic options including blinatumomab, inotuzumab ozogamicin, and CD19 CAR-T therapy has changed the role of allogeneic hematopoietic stem cell transplant (alloHSCT) and intensive chemotherapy. To avoid toxicity from the historical treatment strategies, a more individualized, targeted approach to therapy including detection and monitoring of measurable residual disease (MRD) has become of interest.

Summary The treatment of patients with Ph+ ALL has been rapidly evolving with a more individualized, targeted treatment and use of TKIs and novel therapy.

Keywords Philadelphia chromosome · ALL · Tyrosine kinase inhibitor · Stem cell transplant · Minimal residual disease

Introduction

The Philadelphia chromosome, a translocation between chromosomes 9 and 22, is the most common chromosome abnormality in patients with acute lymphoblastic leukemia (ALL) [1]. Philadelphia chromosome–positive (Ph+) ALL accounts for about 25% of all ALL cases in adults [2]. Before the introduction of tyrosine kinase inhibitors (TKIs), Ph+ ALL was associated with a poor prognosis with limited response to standard cytotoxic chemotherapy and a high relapse rate [3–6]. Allogeneic hematopoietic stem cell transplant (alloHSCT) was performed as a standard of care in all adults at complete remission (CR), but this was limited by the availability of donors and the tolerability of the procedure [7].

The successful introduction of imatinib in the therapeutic strategies designed for the treatment of patients with Ph+ ALL, revolutionized treatment of Ph+ ALL, and improved outcomes significantly [7, 8]. More potent TKIs demonstrated higher CR rate and possibility of long-term effective control of the disease [9, 10]. Novel therapies including blinatumomab, inotuzumab ozogamicin, and CD-19 CAR-T therapy have also provided more effective options for the treatment of relapsed/refractory patients. Accordingly, the role of alloHSCT in this disease has transformed. Since the introduction of TKIs, more patients with Ph+ ALL are eligible to proceed to an alloHSCT and their overall outcomes have improved. However, alloHSCT is not considered the only curative treatment option for many patients. In this review, we will go over the current understanding of treatment of Ph+ ALL including TKIs, novel therapies, and current understanding and role of alloHSCT.

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First-Generation Tyrosine Kinase Inhibitor: Imatinib

Prior to the introduction of TKIs, the majority of patients with Ph+ ALL treated with conventional chemotherapy had poor long-term outcomes. Only about two-third of patients achieved complete response (CR) with 5-year overall survival (OS) from 8 to 12% regardless of chemotherapy regimen [11–17]. The highest CR rate was reported at 92% in a study with chemo regimen of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with cytarabine and methotrexate (hyper-CVAD) [11]. The study included 48 patients with newly diagnosed Ph+ ALL (median age 40 years, range 15–92). Despite of high CR rate, 5-year OS remained poor at 12%, which was similar to that reported in other trials using different regimens [15, 17].

Imatinib is the first-generation tyrosine kinase inhibitor that blocked the activation of downstream proliferation signals from BCR-ABL1 oncoprotein derived from the translocation 9 and 22 [18]. It binds to the adenosine triphosphate (ATP) site of the BCR-ABL1 oncoprotein. The use of imatinib alone in Ph+ ALL, however, was associated with limited efficacy [19]. Therefore, imatinib was studied in combination with chemotherapy. Several studies with different dosing and schedules showed improved outcomes with an acceptable safety profile. CR was achieved in 91 to 98% of patients, and 5-year OS was significantly improved to up to 50% (Table 1).

In the UKALLXII/ECOG2993 study which treated 266 patients of newly diagnosed Ph+ ALL (median age 42 years, range 19–63), the introduction of imatinib resulted in CR rate of 92% and 4-year OS at 38%. This was significantly better than the pre-imatinib cohort with 82% CR rate and 22% 4-year OS, respectively (p = .004) [7]. A phase 2 trial with imatinib and hyper-CVAD treatment in 54 patients with newly diagnosed Ph+ ALL (median age 51 years, range 17–84) demonstrated great safety and efficacy of imatinib when used with chemotherapy [9]. During the early stages of the study, the daily dose was 400 mg of imatinib given from days 1 to 14 of each cycle of intensive chemotherapy, and then 600 mg daily throughout maintenance. The safety profile with initial dose was comparable to hyper-CVAD alone. Therefore, the daily dose was increased to 600 mg from days 1 to 14 during induction/consolidation cycles. This was subsequently adjusted to 600 mg from days 1 to 14 of first course of intensive chemotherapy, followed by 600 mg daily during course 2 to 8 and 800 mg daily during maintenance. The study showed CR rate of 93% and complete molecular response (CMR, defined as the absence of a detectable *BCR-ABL1* transcripts by RT-PCR) of 45% at 3 months. Five-year OS was high at 43% although only 30% of patients underwent subsequent allogenic HSCT in first complete remission (CR1).

The GRAAPH-2005 trial showed that reduced-intensity chemotherapy is comparable treatment response and survival to a high-intensity regimen, both when used in combination with imatinib [28]. Two hundred sixty-eight patients with newly diagnosed Ph+ ALL (median age 47 years, range 18–59) were assigned to reduced-intensity chemotherapy (vincristine and dexamethasone) with imatinib 800 mg daily from days 1 to 28, or to hyper-CVAD with imatinib 800 mg daily from days 1 to 14. Patients in both arms received the same consolidation together with imatinib from days 1 to 14 for each cycle. The CR rates were higher in the reduced-intensity chemotherapy arm with imatinib at 98% compared to high-intensity chemotherapy arm at 91% (p = .006), mainly due to fewer induction deaths in reduced-intensity arm (1% vs 6%, respectively). Five-year OS was 48% and 43% in reduced- and high-intensity arms, respectively (p = .37).

The use of imatinib in combination with reduced-intensity chemotherapy or corticosteroids also improved outcome in older patients by achieving higher CR rates and lower toxicity. In a study with 30 older patients (median age 69 years, range 61–83) treated with the imatinib and prednisone combination, the CR and 2-year OS were reported at 100% and 50%, respectively [24]. Another randomized study in older patients (median age 66 years, range 54–79) showed a higher CR rate (96% vs 50%, p = .0001) with comparable 2-year OS (42%) in patients who received combination of imatinib and reduced-intensity chemotherapy compared to standard chemotherapy [23].

Despite such improved clinical outcome by imatinib treatment, relapse due to the emergence of resistant clones is common in a significant number of patients [38–42]. A study showed that imatinib-resistant mutation is detected about 40% before treatment, which goes up to 80% at time of relapse [43]. Therefore, second- and third-generation TKIs may be substituted for imatinib to overcome the challenges of resistance to imatinib.

Second-Generation Tyrosine Kinase Inhibitors: Dasatinib, Bosutinib, and Nilotinib

Dasatinib

Dasatinib is a BCR-ABL inhibitor that is about 325 times more potent than imatinib. It has additional inhibitory activity in SRC family kinases and c-kit [44, 45]. Dasatinib showed efficacy in patients with imatinib resistance except for patients with T315I mutation [46]. T315I mutation is a gatekeeper mutation in BCR-ABL kinase domain that alters ATP-binding pocket structure and prevents binding of first- and second-generation TKIs [47]. A phase 2 study with single-agent dasatinib 140 mg daily dose in 36 imatinib-resistant Ph+ ALL patients (median age 46 years, range 15–85) demonstrated good efficacy with 42% (n = 15) major hematologic responses (defined as a best hematologic response of complete

Table 1 The characteristics and outcome of frontline trials using TKIs in Ph+ ALL patients

TKI	Age-specific indication	Chemo regimen/protocol	Intensity	Clinical trial (year)	*N*	median age, [range]	TKI dose (daily, mg/d)	CR (%)	CMR (%)	HSCT at CR (%)	OS (%)
Imatinib		JALSG ALL202	High	Yananda (2006) [20] Hatta (update, 2018) [21]	80	48 [15–63]	600	96	26 (at CR) 72	49 60	76 (12 mo) 50 (60 mo)
		GMALL	High	Wassman (2006) [22]	45	41 [19–63]	400	96	27 (at CR)	80	43 (24 mo)
	Older	GMALL	Low	Ottmann (2007) [23]	28	66 [54–79]	400	96	71 (at 3 mo)	0	42 (24 mo)
	Older	GIMEMA LAL0201-B Steroid	Steroid	Vignetti (2007) [24]	30	69 [61–83]	800	100	4	NA	74 (12 mo), 50 (24 mo)
		GRAAPH 2003	High	De Labarthe (2007) [25] Tanguy-Schmidt (update, 2013) [26]	45	45 [16–59]	600-800	96	NA	49	51 (18 mo) 52 (48 mo)
		NILG	High	Bassan (2010) [27]	59	45 [20–66]	600	92	40 (at 3 mo)	72	38 (60 mo)
		UKALLXII/ECOG2993	High	Fielding (2014) [7]	175	42 [16–64]	400-600	92	NA	46	38 (48 mo)
		Hyper-CVAD	High	Daver (2015) [9]	54	51 [17–84]	400-800	93	45 (at 3 mo)	30	43 (60 mo)
		GRAAPH 2005 Vincristine/Dexamethasone	Low	Chalandon (2015) [28]	135	49 [18–59]	800	98	29 (at 3 mo)	74	48 (60 mo)
		GRAAPH2005 Hyper-CVAD	High	Chalandon (2015) [28]	133	45 [21–59]	800	91	23 (at 3 mo)	79	43 (60 mo)
		Multiagent chemo	High	Lim (2015) [29]	87	41 [16–71]	600	94	66 (at CR)	64	33 (60 mo)
Dasatinib		GIMEMA LAL1205 Prednisone	Steroid	Foa (2011) [30]	53	54 [24–76]	100-140	93	22 (at CR)	NA	69 (20 mo)
		Hyper-CVAD	High	Ravandi (2015) [10]	72	55 [21–80]	100	96	65 (at 3 mo)	17	46 (60 mo)
		GIMEMA LAL 1509 Corticosteroid with or without chemotherapy	Steroid or steroid+ low	Chiaretti (2015) [31]	60	42 [19–59]	140	97	19 (day 85)	NA	58 (36 mo)
		Hyper-CVAD	High	Ravandi (2016) [32]	94	44 [20–60]	70-100	88	NA	47	69 (36 mo)
	Older	EWALL-Ph-01 Vincristine and dexamethasone	Low	Rousselot (2016) [33]	71	69 [55–83]	140	97	24 (at consolidation)	10	36 (60 mo)
Nilotinib	Older	EWALL-Ph-02	Low	Ottmann (2014) [34]	47	65 [55–85]	800	87	NA	20	67 (24 mo)
		Multiagent chemo	High	Kim (2015) [35]	90	47 [17–71]	800	91	77 (at 3 mo)	63	72 (24 mo)
Ponatinib		Hyper-CVAD	High	Jabbour (2015) [36••]	64	48 [21–80]	30-45	100	77 (at 3 mo)	16	78 (36 mo)
	Older	GIMEMA LAL1811 Corticosteroid	Steroid	Martinelli (2017) [37]	42	68 [27–85]	45	95	46 (at 6 mo)	NA	87 (12 mo)

Ph+ ALL, Philadelphia chromosome–positive acute lymphoblastic leukemia; *TKI*, tyrosine kinase inhibitor; *CR,* complete remission; *CMR,* complete molecular remission; *HSCT,* hematopoietic stem cell transplant; *JALSG,* Japan Adult Leukemia Study Group; *GMALL,* German Multicentric Study Group for Adult ALL; *GIMEMA,* Gruppo Italiano Malattie Ematologiche dell'Adulto; *GRAAPH,* Group for Research on Adult Acute Lymphoblastic Leukemia; *NILG,* Northern Italy Leukemia Group; *hyper-CVAD,* hyper fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with cytarabine and methotrexate; *EWALL,* European Working Group on adult ALL

hematologic response or no evidence of leukemia) and 58% (n = 21) complete cytogenetic remission (CCyR, defined by absence of Ph-positive metaphases in a bone marrow sample of approximately 20 metaphases) [48].

A number of trials have been conducted in the frontline setting combining dasatinib with various chemotherapy regimens. A phase 2 trial by Ravandi et al. which studied dasatinib 50 mg twice daily in combination with hyper-CVAD showed high efficacy with durable remissions. Of 72 newly diagnosed patients with Ph+ ALL (median age 55, range 21–80), 96% achieved CR with 83% of those achieving a complete cytogenetic response (CCyR) and complete molecular response (CMR) in 65%. The 5-year relapse-free survival (RFS) and OS were 44% and 46%, respectively [10]. Thirty-one percent (n = 22) of patients relapsed, and 8 patients had isolated central nervous system (CNS) relapse. The SWOG S0805 with 97 newly diagnosed, young patients (median 44 years, range 20–60) showed high efficacy for the combination of dasatinib and chemotherapy followed by alloHSCT in younger patients [32]. Patients were designed to receive hyper-CVAD plus dasatinib, alloHSCT at CR1, followed by maintenance dasatinib from post-transplant day 100, indefinitely. The overall response rate including CR and CRi was 88%. Forty-nine percent (n = 41) of patients received alloHSCT in CR1. The 3-year RFS was 62% and OS was 69%.

Several studies investigated the combination of dasatinib with lower intensity therapy. In the CALGB study 10701, 64 patients (median age 60 years, range 22–87) with newly diagnosed Ph+ ALL received the combination of dasatinib and prednisone used for induction, HSCT, or chemotherapy, followed by dasatinib maintenance [49]. The study reported a CR rate of 97%, 3-year OS of 55%, and DFS of 43%. In the EWALL-PH-01 trial, 71 elderly patients (median age 69 years, range 59–83) received induction with dasatinib (100–140 mg daily), low-intensity chemotherapy including vincristine and dexamethasone, followed by minimal chemotherapy for consolidation with a regimen of L-asparaginase, high-dose methotrexate, and intermediate-dose cytarabine [33]. CR was reported in 96% with 65% achieving MMR; however, the 5-year RFS and OS were 28% and 36%, respectively. In this study, only 10% of patients underwent allogenic HSCT.

GIMEMA LAL1509 trial demonstrated the effectiveness of dasatinib for chemo-free induction [30]. Fifty-three patients (median age 54 years, range 24–76) with newly diagnosed Ph+ ALL underwent induction with dasatinib for 84 days, prednisone for 32 days, and intrathecal chemotherapy. Forty-nine (92.5%) patients achieved CR at day 22. More patients achieved major molecular remission (MMR) which increased with time: 22% at day 22 and up to 52% at the end of induction on day 85. Only 60% patients received consolidation after CR, but RFS and OS at 20 months were high at 51% and 69%, respectively.

Dasatinib overcomes frequent imatinib-resistant mutations in the P-loop region, except for T315I [46]. In dasatinib-treated patients, T315I mutation is seen frequently at relapse. In the trial of dasatinib in combination with hyper-CVAD, 22 of 72 (30.5%) patients relapsed [10]. Among 13 patients with available results for ABL mutations, 54% (n = 7) developed resistance-associated mutations including 4 T315I, 2 V299L, and 1 F359V. Other trials have also reported the high incidence of T315 mutations at relapse including 6 of 8 patients (75%) in the CALGB study 10701, 24 of 36 patients (75%) in the EWALL-Ph-01 trial, and 12 of 17 patients (71%) in the GIMEMA LAL1509 study [30, 33, 49].

Nilotinib

Nilotinib is another second-generation TKI with better selectivity and affinity to ABL1 kinase, compared to imatinib [50, 51]. The initial phase 2 trial studied single-agent nilotinib (800 mg daily) in 44 patients with Ph+ ALL (median age 46, range 18–75) refractory to imatinib with a reported CR rate of 24% [52]. Mutations of E255V, Y253H, or T315I have been reported to be resistant to nilotinib [53, 54].

Several trials have studied nilotinib in combination with chemotherapy for newly diagnosed patients with Ph+ ALL. A phase 2 study with multiagent chemotherapy combined with nilotinib in 90 patients with newly diagnosed Ph+ ALL (median age 47 years, range 17–71) reported a 91% CR rate with OS and RFS at 2 years being 72% and 72%, respectively [35]. EWALL-Ph-02 study treated older patients with newly diagnosed Ph+ ALL (median age 65, range 55–85) with combination of nilotinib and an age-adjusted low-intensity regimen [34]. The investigators have reported a CR rate of 87%, and 2-year OS of 67% at a median follow-up of 8.5 months.

The drug has not been approved for Ph+ ALL patients, but a number of clinical studies, including NCT01914484 (completed), NCT02611492, and NCT02253277 (completed), are investigating the potential utility of nilotinib in patients with Ph+ ALL.

Bosutinib

Bosutinib is a dual SRC and ABL kinase inhibitor with approximately 200 times higher potency compared to imatinib [55]. Bosutinib has a good safety profile with less vascular or cardiac adverse events in long-term use compared to other TKIs [56, 57]. This is possibly related to minimal inhibition of c-KIT and platelet-derived growth factor receptor (PDGF-R) [58]. A phase 1,2 study of bosutinib in combination with inotuzumab ozogamicin for patients with relapsed Ph+ ALL is ongoing (NCT02311998).

Compared to imatinib, second-generation TKIs have better efficacy overall with increased ability to overcome mutations associated with resistance. However, relapse from resistance

remains a problem with second-generation TKIs [59]. The T315I mutation, often detected at relapse, is resistant to all second-generation TKIs.

Third-generation TKI—Ponatinib

Ponatinib was developed to overcome challenges leading to relapse while using the prior TKIs. Ponatinib is a third-generation TKI with pan-BCR-ABL1 inhibition activity. Ponatinib is about 520 times more potent in inhibiting native ABL compared to imatinib, with additional benefits from its activity against other kinases including fibroblast growth factor receptor, VEGF, SRC, KIT, and FLT3 [60, 61].

Ponatinib has demonstrated significant activity in patients with resistance to second-generation TKI or with T315I mutation [62]. It was approved by FDA in 2012 for patients with resistance or intolerance to prior TKI treatment, including patients with T315I mutation. A phase 2 study of ponatinib as a salvage therapy showed high efficacy regardless of T315I mutation status [62]. In 32 patients with Ph+ ALL who either had T315I mutation or were resistant or intolerant to dasatinib and nilotinib, CCyR was achieved in 38% and major cytogenetic response was achieved in 47%. Estimated PFS and OS at 12 months were 7% and 40%.

There are few studies available that have compared the efficacy of ponatinib to prior TKIs. A retrospective, propensity-score matching analysis compared the outcome of patients in two phase 2 trials: combining hyper-CVAD with ponatinib (n = 47), or dasatinib (n = 63) [63]. Better outcomes were reported with ponatinib compared to dasatinib: 3-year survival in the ponatinib trial was 83% compared to 56% in the dasatinib trial (p = .03). Three-year EFS was 69% in the ponatinib trial, compared to 46% in the dasatinib trial (p = .04). Patients receiving ponatinib also had a higher negative MRD at the end of induction on day 21. CCyR and MMR both at CR and at 3 months were higher in ponatinib trial. There was no difference in cause of mortalities between 2 arms.

Jabbour et al. reported high response rate using combination of ponatinib and hyper-CVAD in 76 patients (median age 47 years, IQR 39–61) with newly diagnosed Ph+ ALL [36••, 64]. Initially, the ponatinib dose was 45 mg per day for the first 14 days of cycle 1 and then continuously at 45 mg per day for the subsequent cycles. Due to increased vascular events (2 cardiovascular deaths attributed to ponatinib), the dose was changed to 30 mg daily after achieving CR, and 15 mg daily after achieving CMR. Ponatinib daily was continued indefinitely. Maintenance with vincristine (2 mg IV on day 1) and prednisone (200 mg orally on days 1 to 5) was given monthly for 2 years. Following these adjustments, 100% of patients have achieved CR, 97% (n = 74) MMR, and 83% (n = 63) CMR. Three-year EFS and OS were 70% and 76%, respectively. Ten patients (16%) underwent ASCT in CR1, and median OS was similar regardless of censoring at ASCT. Only 7 patients relapsed. The recent update on the study showed 5-year EFS and OS at 68% and 74%, respectively [65•].

Combination of ponatinib with prednisone in older patients has also been reported to achieve a CMR rate at 46%, higher than what has been reported with other TKIs. In the GIMEMA LAL1811, a phase 2 study of ponatinib plus steroid in older patients with newly diagnosed Ph+ ALL (n = 42, median age 68, range 27–85), CMR was achieved in 46% with the 1-year OS at 88% [37]. Ponatinib dose was 45 mg daily, but 31% of patients had serious adverse events with 1 ponatinib-related mortality. Only 15 patients continued the same dose at week 24. Therefore, dose de-escalation based on response is likely important when using ponatinib. A large randomized trial (NCT 03589326) is currently ongoing to compare ponatinib and imatinib in combination to reduced-intensity chemotherapy.

Novel Therapeutics—Blinatumomab, Inotuzumab Ozogamicin, and CAR-T

Blinatumomab

Leukemic cells in B-cell ALL commonly express cell surface antigens including CD19, CD20, and CD22. These can be utilized as targets for antibody-based therapy. Blinatumomab is a bispecific T-cell engager (BiTE) targeting CD3 on the surface of T-cells and CD19 on ALL blasts [66]. It activates autologous cytotoxic T cells by linking them to tumor cells [66]. Blinatumomab was approved by FDA with the indication for relapsed or refractory (R/R) ALL [67••].

A phase 2 study (ALCANTARA) of blinatumomab in 45 patients (median age 55 years, range 23–78) with R/R Ph+ ALL demonstrated significant efficacy and acceptable safety [68•]. The included patients were heavily treated including 23 (51%) (n =23) with prior ponatinib therapy; furthermore, 44% (n = 20) had prior HSCT, and 27% (10 of 37 tested) had T315I mutation. Among the 45 patients treated, 36% (n = 16) achieved CR/CRi during the first two cycles. Among the patients with CR/CRi, 88% achieved complete molecular response. Seven patients underwent alloHSCT. Median RFS was 6.7 months, and median OS was 7.1 months.

A retrospective study of 12 cases of R/R leukemia from MD Anderson Cancer Center demonstrated good safety and efficacy of blinatumomab in combination with TKIs [69]. Nine patients with Ph+ ALL and 3 patients with chronic myeloid leukemia in blast phase (median age 65 years, range 30–77) were reported. CR was achieved in 50%, with CCyR in 71%, and molecular response in 75%. Overall survival at 6 and 12 months were 73%. Another retrospective study of 11 patients with previously treated Ph+ ALL demonstrated safety and efficacy of blinatumomab with concurrent use of TKIs as

consolidation regimen [70]. Eight of 9 patients with persistent MRD achieved CMR (response after a median of one cycle), and 2 of 2 patients without measurable disease maintained CMR. A propensity score analysis in trials of patients with R/R Ph+ ALL suggested a better outcome for patients treated with blinatumomab (45 patients) compared to standard chemotherapy (55 patients) including higher response rates (36% vs 25%, $p = .076$ at Bayesian data augmentation) and longer OS (median 7.1 months vs 6.0 months, HR 0.77 (95% CI 0.61–0.96), $p = .031$) [71•].

Blinatumomab has also been investigated in newly diagnosed patients. A recently published phase 2 study from the GIMEMA group evaluated 63 patients with newly diagnosed Ph+ ALL (median age 54 years, range 24–82) treated with dasatinib plus steroids followed by 2 cycles of blinatumomab [72••]. Ninety-eight percent achieved CR. Twenty-nine percent had a complete molecular response after dasatinib induction, which was increased to 60% after 2 cycles of blinatumomab. With median follow-up of 18 months, overall survival and disease-free survival were 95% and 88%, respectively. Twenty-four patients underwent an alloHSCT in first CR.

More studies are currently ongoing using the combination of blinatumomab and TKI with or without chemotherapy—including NCT02143414, NCT03263572, NCT 04329325, and NCT03147612.

Inotuzumab Ozogamicin

Inotuzumab ozogamicin (InO) is an anti-CD22 antibody conjugated with a DNA-binding cytotoxic agent, calicheamicin. In INO-VATE trial, a phase 3 trial with 208 patients with R/R B-cell ALL, single-agent InO showed better safety and efficacy compared to standard chemotherapy [73]. Patients who received InO had higher response at 81% compared to 29% in patients who received standard chemotherapy ($p < .001$). The patients who received InO had longer median DFS of 5 months and median OS of 7.7 months, compared to 1.8 months and 6.7 months, respectively, for those who received standard chemotherapy ($p = .03$ and $p < .001$). In a recent update of the study, the InO arm had a higher 2-year OS (22.8% vs 10.0%, 1-sided $p = .0105$) [74]. The trial included a total of 30 patients with Ph+ ALL, and use of InO was associated with a higher CR/CRi rate (78% vs 44%, $p = .08$) [73]. In a phase 1,2 study of InO in patients with R/R CD22+ ALL, 16 patients with Ph+ ALL were included and 9 (56%) achieved CR/CRi, including 25% ($n = 4$) with CR; 100% of responders achieved MRD negativity [75, 76]. The median OS was 7.4 months, and median PFS was 4.4 months.

In a phase 1 and 2 trial of patients with R/R Ph+ ALL excluding T315I mutation (NCT02311998) combining InO and bosutinib, 14 patients (median age 62 years, range 19–74) were treated and 79% achieved CR/CRi rate with 55% achieving CMR [77]. Median EFS and OS were 8.1 months and 8.2 months, respectively. This study showed that combination of InO and TKIs is safe although further studies are warranted. Combining ponatinib with InO has been associated with concerns related to the overlapping hepatotoxicity, but given the high efficacy of ponatinib, future studies may be warranted.

CAR-T cells

CD19-directed chimeric antigen receptor (CAR) T has been approved for the treatment of pediatric patients with relapsed precursor B-ALL [78, 79]. CD19-directed chimeric antigen receptor (CAR) T cells have been actively studied in the setting of refractory B-ALL [79–82••]. An early phase 1 trial of CD19 CAR T cells in 16 patients including 4 with Ph+ ALL demonstrated efficacy [83]. In a recent phase 1 trial of CD19 CAR-T therapy in patients with relapsed B-cell ALL, 16 of 53 patients (30%) had Ph+ ALL with a median of 2.5 (range, 1–4) prior TKIs [82••]. Five patients had T315I ABL kinase mutations. Ninety-three percent achieved CR. The survival outcome for patients with Ph+ ALL patients was not reported separately, but no survival difference with Ph-negative ALL patients was reported in the study. In total, at a median follow-up of 29 months, median EFS and OS were 6.1 months and 12.9 months, respectively. Multiple trials including NCT04206943 are ongoing to identify the role of CAR-T cells in ALL including Ph+ ALL patients.

Stem Cell Transplant

AlloHSCT has been historically established as a standard treatment option for younger, fit patients with a matched donor. AlloHSCT in CR1 has been the standard therapy in Ph+ ALL.

Multiple studies showed benefit of alloHSCT in younger patients. In UKMRCALLXII/ECOG2993 trial with 267 patients with Ph+ ALL (median age 40 years, range 15–60), 82% achieved CR [84]. Twenty-eight percent underwent alloHSCT in CR1, and this patient group showed superior survival outcome compared to patients receiving chemotherapy alone, with 5-year survival at 44% (sibling donor) and 36% (matched unrelated donor). SWOG0805 trial also demonstrated relapse-free and overall-survival benefit at 175 days posttransplant [32]. The GRAAPH-2005 study that compared low-intensity induction with imatininb, vincristine, steroid to hyper-CVAD plus imatinib in younger patients also demonstrated a survival benefit for patients undergoing alloHSCT in CR1 [28].

The role of alloHSCT for Ph+ ALL in current TKI era is evolving. The TKI use has shown survival benefit in patients undergoing alloHSCT, and more patients have become eligible for alloHSCT [7, 21, 85]. The GRAAPH-2005 patients with available matched donors were designed to proceed to

alloHSCT in CR1 and 63% of patients underwent alloHSCT. The patients who achieved MMR after cycle 2 had a similar outcome to patients who received alloHSCT. There are no randomized trials to date comparing the outcomes of patients with or without alloHSCT.

The potential benefit of TKI maintenance after alloHSCT is an important question to address. However, most studies to date are limited to retrospective data [86]. The randomized trial from GMALL study group investigated imatinib use in 55 patients after alloHSCT and compared prophylactic use with preemptive use triggered by MRD positivity [87]. Prophylactic use of imatinib was associated with a lower rate of molecular recurrence (40% vs 69%, $p = .046$), but there was no difference in OS (80% vs 75%) between 2 groups. Overall, patients had a high survival rate despite the low proportion of patients who continued imatinib. In a recent large retrospective study of 165 post-transplant patients, prophylactic TKI maintenance showed better PFS ($p = .041$), and lower relapse rate in patients who received TKI over 24 months compared to less than 24 months (HR 0.12, $p = .045$) [88•]. The study included patients who received newer generation of TKIs than imatinib as maintenance treatment, and it suggested that newer generation of TKIs may have additional benefit of reduction in relapse rate in preemptive use.

Several studies have examined the outcomes of patients based on early achievement of molecular response. The study by the Korean group examining the role of nilotinib in the frontline setting suggested that MRD status after remission predicts survival regardless of alloHSCT [35]. In patients who achieved CMR, there was no significant difference in OS and molecular RFS after 2 years in patients whether or not they received alloHSCT. Other studies have shown that MRD status is a prognostic marker for relapse and survival in patients with Ph+ ALL [89, 90].

Achieving MRD negative status has been extensively studied for risk stratification to spare HSCT and avoid toxicity in the era of TKIs. Short and colleagues have reported that patients achieving CMR at 3 months after the combination of hyper-CVAD and a TKI and without alloHSCT in first remission had a favorable 4-year OS at 66% [91]. The combination of hyper-CVAD plus ponatinib without alloHSCT has reported an overall CMR at 84% and estimated 5-year OS at 73%. These reports suggest that patients with early deep responses might not require alloHSCT in first CR.

Conclusion

The treatment of patients with Ph+ ALL has been rapidly evolving with the incorporation of more potent TKIs and novel treatment strategies including blinatumomab, InO, and CAR-T therapies. This has led to the possibility of a more individualized approach with the focus on the reduction of toxicity associated with chemotherapy and alloHSCT. In the future, studies with potent TKIs combined to de-intensified chemotherapy with or without antibodies may further refine our treatment strategies. Preclinical studies have suggested that TKI activity can be enhanced by BCL-2 inhibitor, venetoclax [92]. A trial with regimen of venetoclax, ponatinib, and steroid in Ph+ ALL in refractory or relapsed setting is ongoing (NCT03576547). Approaches including alloHSCT selection can be more individualized by better risk stratification using MRD monitoring. Ongoing clinical studies would likely help to further optimize the treatment of patients with Ph+ ALL.

Declarations

Conflict of Interest Kunhwa Kim declares that she has no conflict of interest. Elias Jabbour has received research funding and compensation for service as a consultant from Amgen, AbbVie, Adaptive Biotechnologies, Bristol-Myers Squibb, Genentech, Pfizer, Takeda, and Ascentage Pharma. Nicholas J. Short has received research funding from Takeda Oncology and Astellas; has received compensation for service as a consultant from Takeda Oncology and AstraZeneca; and has received honoraria from Amgen. Partow Kebriaei has received research funding from Amgen and Ziopharm; has received compensation for service as a consultant from Jazz Pharmaceuticals; and has participated on advisory boards for Pfizer, Kite Pharma, and Novartis. Hagop Kantarjian has received research funding from AbbVie, Amgen, Ascentage Pharma, Bristol-Myers Squibb, Daiichi Sankyo, ImmunoGen, Jazz Pharmaceuticals, Novartis, Pfizer, and Sanofi; has received honoraria from AbbVie, Amgen, Daiichi Sankyo, Novartis, Pfizer, Adaptive Biotechnologies, Aptitude Health, Bio Ascend, Delta-Fly Pharma, Janssen Global, Oxford Biomedical Technologies, and Takeda; and has served on an advisory board for Actinium Pharmaceuticals. Farhad Ravandi has received research funding from Bristol-Myers Squibb, and has received compensation for service as a consultant from Bristol-Myers Squibb, Novartis, Pfizer, and Takeda.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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