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Leukemia (PH Wiernik, Section Editor)

Treatment of Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

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Opinion statement

With the introduction of tyrosine kinase inhibitors (TKIs) in the management of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), the prognosis of patients has improved dramatically. Currently, the standard of care in the frontline setting for fit patients is TKI in combination with chemotherapy. Age-adjusted chemotherapy or corticosteroids alone have been used with TKIs in elderly patients with comorbidities with modest long-term benefit. The primary goal of treatment is the achievement of early deep molecular remission as the achievement of complete molecular remission (CMR) at 3 months has been demonstrated to be predictive of higher long-term survival. The probability of attaining this goal by a more potent TKIs like dasatinib or ponatinib is higher, thus we recommend the use of second- or third-generation TKIs over imatinib. Clinicians should be aware of possible fatal cardiovascular events mainly related to ponatinib. Allogeneic hematopoietic stem cell transplantation (alloHSCT) should still be considered in first remission, especially for younger patients treated with imatinib combination therapy. A subset of patients achieving CMR at 3 months may be able to continue consolidation and maintenance with chemotherapy and TKI without the need for alloHSCT. Because of higher risk of relapses in the central nervous system, intrathecal chemoprophylaxis is mandatory for all patients. New strategies incorporating novel agents, such as antibody-drug conjugates, bispecific monoclonal antibodies, potent TKIs, and CAR T cells are under investigation.

Introduction

The Philadelphia chromosome (Ph) is the most common chromosomal abnormality in adult acute lymphoblastic leukemia (ALL), and represents an independent risk factor with inferior outcomes compared to Ph chromosome-negative (Ph−) ALL patients [1]. The incidence of Ph chromosome-positive (Ph+) ALL increases with age, reaching 50% in patients older than 60 years [2]. Historically, adult patients with Ph+ ALL treated with standard chemotherapy regimens alone had very poor outcomes. Despite high rates of complete remission (CR) with induction chemotherapy reaching up to 90%, the duration of remission was short and the 5-year overall survival (OS) did not exceed 20% [3, 4]. The understanding of the pathophysiology of Ph+ leukemias and the role of BCR-ABL1 oncoprotein in leukemogenesis paved the way for the discovery of imatinib mesylate, the first-generation tyrosine kinase inhibitor (TKI) capable of blocking the adenosine triphosphate (ATP) binding site of BCR-ABL1 oncoprotein and preventing the activation of downstream proliferative and survival pathways [5, 6]. Since the discovery of imatinib, ongoing research has significantly changed the landscape of therapy of Ph+ ALL. In this review, we will discuss different treatment options for adult Ph+ ALL and offer some future directions and perspectives in optimizing long-term outcomes.

Treatment options

First-generation tyrosine kinase inhibitor: imatinib

The introduction of imatinib transformed the treatment of adult patients with Ph+ ALL. Although single agent activity was modest and not durable [7], the combination of imatinib with standard chemotherapy regimens in the frontline setting marked the beginning of a new era. The combination was generally safe, and yielded CR rates between 91 and 98% with an unprecedented 5-year OS rate of up to 50% [8–15]. In an updated single-institution phase 2 trial combining imatinib with hyperfractionated cyclophosphamide, vincristine, Adriamycin, and dexamethasone (hyper-CVAD) chemotherapy, 54 older patients with a median age of 51 years (range, 17–84) were treated. The CR rate was 93% with a complete molecular remission (CMR) at 3 months of 45%. Despite a low proportion of patients (30%) undergoing subsequent allogeneic hematopoietic stem cell transplantation (alloHSCT) in first remission (CR1), the 5-year OS was 43%, remarkably better than historical controls [13]. Early and concomitant administration of imatinib with chemotherapy has since been incorporated into various standard regimens used to treat newly diagnosed adult patients with Ph+ ALL. The UKALLXII/ECOG2993 study evaluated 441 adult patients newly diagnosed with Ph+ ALL with a median age of 42 years (range, 16–64). Patients were enrolled into 3 consecutive cohorts, 266 patients in the pre-imatinib cohort, 86 in the late imatinib cohort in which imatinib was introduced as single agent after 2 induction courses, and 89 in the early imatinib cohort in which imatinib was added to the second phase of induction. Authors reported a higher CR rate in the imatinib cohort compared to pre-imatinib cohort (92% versus 82% respectively, $p = 0.004$), and an improved 4-year OS (38% versus 22% respectively, $p = 0.003$). The early introduction of imatinib further improved outcomes with a 4-year OS of 43%. The authors suggested that improvement in survival was in part related to the higher rate of alloHSCT with imatinib (46% in the imatinib cohort versus 31% in the pre-imatinib

cohort) [11]. Combining imatinib with reduced-intensity chemotherapy is also feasible, and is capable of achieving a high CR rate and allowing the transition to alloHSCT in CR1. In the GRAAPH-2005 trial, 268 adult Ph+ ALL patients with a median age of 47 years (range,18–59) were randomized to either imatinib (400 mg twice daily from day 1–28) combined with reduced-intensity chemotherapy (vincristine and dexamethasone) or imatinib (400 mg twice daily from days 1–14) with hyper-CVAD chemotherapy during induction course [12]. The CR rate was higher in lower-intensity chemotherapy compared to hyper-CVAD (98% versus 91% respectively, $p = 0.006$), mainly attributed to differences in induction deaths (1% versus 6% respectively). Among responders, 63% underwent alloHSCT and 14% had autologous HSCT (autoHSCT). With a median follow-up of 4.8 years, the 5-year event-free survival (EFS) and OS were 37% and 46% respectively, with no differences between the two groups [12].

Development of secondary resistance to imatinib has led to the development of a number of second- and third-generation TKIs designed to overcome the resistance mechanisms.

Second-generation tyrosine kinase inhibitor: dasatinib and nilotinib

Dasatinib is a second-generation multikinase inhibitor of BCR-ABL1 in both active and inactive forms. Its activity is less dependent on P-loop interactions for drug binding, overcoming most of the imatinib-resistant kinase domain mutations, except for T315I mutation [16, 17]. Dasatinib showed initial activity as single agent in patients with Ph+ ALL resistant or intolerant to imatinib [18–20]. In a phase 2 trial, 58% of patients with Ph+ ALL resistant or intolerant to imatinib achieved complete cytogenetic remission (CCyR) with single agent dasatinib 140 mg orally daily [18]. Another international phase 2 trial showed both major hematologic and cytogenetic responses in 35% and 52% respectively of patients with imatinib-resistant or -intolerant CML in lymphoid blast phase [19]. Observed responses, however, were short-lived with a median progression-free survival (PFS) of only 3 months. Ravandi et al. combined dasatinib with standard chemotherapy in the frontline setting. In a single-institution phase 2 trial, 72 newly diagnosed Ph+ ALL patients with a median age of 55 years (range, 21–80) were treated with hyper-CVAD chemotherapy in combination with dasatinib (100 mg daily for the first 14 days, then 70 mg daily continuously with consolidation and maintenance cycles). The CR rate was 96%, with CCyR and CMR achieved in 83% and 65%, respectively. The 5-year relapse-free survival (RFS) and OS were 44% and 46%, respectively with a median follow-up of 67 months for surviving patients [21•]. The SWOG S0805 study included 97 newly diagnosed Ph+ ALL patients with a median age of 44 years (range, 20–60). Patients received hyper-CVAD chemotherapy with dasatinib followed by alloHSCT in CR1. The overall response rate (ORR) including CR and CR with incomplete count recovery (CRi) was 88%. Forty-one (49%) patients underwent an alloHSCT in CR1. The 3-year RFS and OS were 62% and 69%, respectively [22].

Not all patients can tolerate intensive chemotherapy, mainly because of higher mortality rates related to risks of severe cytopenias and infections in older patients with comorbid conditions. Several studies demonstrated the possibility of long-term survival with acceptable toxicity in elderly patients,

without the need for intensive chemotherapy or alloHSCT [23–25]. The GIMEMA group tested dasatinib 70 mg twice daily combined with only prednisone 10–60 mg/m2 per day and intrathecal chemotherapy for 84 days in patients with newly diagnosed Ph+ ALL. All 53 patients (median age, 54 years, (range, 24–76)) achieved CR. The rate of MMR was continuously increasing with time, starting with 22% at day 22, 33% at day 43, 40% at day 57, and reaching 52% of patients at the end of induction course (day 85). Although only 60% of patients received consolidation chemotherapy after CR, the RFS was 51% at 20 months [23]. Chiaretti et al. reported similar results on 60 patients with newly diagnosed Ph+ ALL with a median age of 42 years (range, 19–59) who were treated with dasatinib 140 mg daily and steroids. At end of induction course (85 days), the CHR rate was 97%, with a sustained CMR achieved in 11 patients (19%). Patients not achieving CMR at end of induction then received chemotherapy and/or alloHSCT. Patients who achieved CMR at day 85 had better disease-free survival (DFS) compared to those with minimal residual disease (MRD) (75% vs 44%, $p = 0.06$). The OS at 3 years was 58%, with a median follow-up of 28 months [24]. The European EWALL-PH-01 international study investigated dasatinib (100–140 mg daily) in combination with low-intensity chemotherapy, consisting of vincristine and dexamethasone during induction, and L-asparaginase, high-dose methotrexate, and intermediate-dose cytarabine in consolidation cycles, in older patients aged 55 years and above. Seventy-one patients with a median age of 69 years (range, 59–83) were enrolled. Despite achieving CR rate in 96% of patients with a MMR rate of 65%, the 5-year RFS and OS were only 28% and 36%, respectively. In this older population, only 10% of patients underwent alloHSCT. These results confirmed the possibility of achieving remission with modest long-term survival in elderly patients without the need of intensive chemotherapy or alloHSCT.

Nilotinib is another second-generation TKI with higher affinity for BCR-ABL1 compared to imatinib [26]. In a multicentric phase 2 trial from Korea, 90 patients with newly diagnosed Ph+ ALL with a median age of 47 years (range, 17–71) were treated with nilotinib 400 mg twice daily in combination with chemotherapy (vincristine, daunorubicin and prednisolone). The CHR was 91% following induction treatment. The cumulative CMR was unprecedentedly high, reaching 94% of responders with 57 patients (70%) proceeding to alloHSCT in CR1. The 2-year RFS and OS were 72% and 72% respectively [27]. Nilotinib in combination with lower-intensity chemotherapy has also been investigated. The EWALL group showed high efficacy in combining low-intensity chemotherapy with nilotinib in patients older than 55 years. Among 56 older patients treated with a median age of 65 years (range, 55–85), 87% achieved CR. With a median follow-up of 8.5 months, the OS was 73% at 2 years without the need of alloHSCT [28]. Recently, Chalandon et al. presented the interim analysis of the GRAAPH-2014 trial [29]. Sixty patients with newly diagnosed Ph+ ALL with a median age of 47 years were treated with low-intensity chemotherapy in combination with nilotinib. The CR rate was 98%, with a cumulative MMR rate after 4 cycles of 93%. Seventy-three percent of patients were able to proceed to alloHSCT in CR1. With a median follow-up of 14 months, the 1-year PFS and OS were estimated at 85% and 96%. This trial will continue to accrue for a total of 265 patients to determine if lower-intensity chemotherapy with nilotinib followed by alloHSCT will lead to better outcomes in younger patients [29].

Third-generation tyrosine kinase inhibitor: ponatinib

It has become evident that patients, who relapse after therapy with imatinib, often acquire kinase domain mutations that confer resistance to imatinib. T315I mutation, noted in some reports in up to 75% of cases of acquired kinase mutations at time of relapse, is known to be less sensitive to all first- and second-generation TKIs [30, 31]. Ponatinib is a third-generation pan-BCR-ABL1 inhibitor with very high potency specifically designed to overcome most of the kinase domain mutations, including T315I [32]. Most interestingly, kinase mutations were found in 37% of patients at time of diagnosis before even the initiation of treatment [31]. Rousselot et al. identified 23% of patients with T315I mutation at diagnosis, which was associated with early relapses. Of 24 patients at time of relapse, 18 (75%) patients were harboring a T315I mutation [25].

Ponatinib as single agent resulted in CCyR in 38% of patients ($N = 32$) with Ph+ ALL resistant to second-generation TKI or harboring T315I mutation. The median duration of response was short at 3 months with an estimated sustained response after 12 months of 8%. The 1-year OS was reported at 40% [33]. Ponatinib in combination with intensive chemotherapy has shown the highest anti-leukemia activity to date in a single-institution phase 2 trial including 37 patients with a median age of 51 years (range, 27–75). Patients were treated with hyper-CVAD chemotherapy in combination with ponatinib at a dose of 45 mg daily for 14 days for the first cycle and then continuously after the second cycle. Due to safety concern related to increased risk of cardiovascular events, the protocol was amended, and ponatinib dose was reduced to 30 mg daily starting with the second cycle, then 15 mg daily indefinitely after CMR is achieved. Adverse events possibly related to ponatinib were seen in 3 patients (8%) with venous thrombotic events, and in another 3 patients (8%) with myocardial infarction; 2 patients died. Other serious adverse events like grade 3–4 liver dysfunction and grade 3 pancreatitis were seen in 37% and 16% respectively. All patients, however, achieved CR and 97% achieved MRD negativity by flow cytometry. The overall CMR rate was 78%. With a median follow-up of 26 months, the estimated 2-year OS was 80% [34••]. Updated results of this trial including 67 patients with a median follow-up of 33 months (range, 2–62) were reported recently. The rate of CR and CMR remains at 97% and 77% respectively [35]. There were no grade ≥ 3 vascular events reported after amendment and dose reduction. Given that ponatinib related adverse events, mainly arterial occlusive events, are related to the dosing of ponatinib, a lower dose of ponatinib would be safer, while still maintaining efficacy [36]. Ponatinib was also used in combination with corticosteroids as frontline therapy in elderly or unfit patients in the GIMEMA LAL 1811 trial. Results on 42 patients with a median age of 69 years (range, 27–85) with untreated Ph+ ALL were recently presented. Patients received ponatinib 45 mg orally daily along with corticosteroids from 14 days prior to therapy until day 29 of the initial cycle. After the first cycle, 95% of patients achieved CHR. Further, the CMR rate was 45.8% higher than what was reported in other studies with dasatinib and corticosteroids. The 1-year OS was 87.5% after a median follow-up of 11.4 months. Serious adverse events related to ponatinib continued to be of concern, with only 35% of patients continued on 45 mg of ponatinib after 24 weeks of therapy [37••].

Table 1. Clinical outcomes of patients newly diagnosed with Ph+ ALL treated with TKI-based therapies

Study (year)	N	Median age, (range)	Regimen	CR, %	CMR, %	AlloSCT in CR1, %	OS, %
Imatinib							
Wassmann (2006) [8]	45	41 [19–63]	GMALL	96	52 (after induction)	80	43 at 24 mo
Bassan (2010) [9]	59	45 [20–66]	NILG 09/00	92	40 (3 mo)	63	38 at 60 mo
Tanguy-Schmidt (2013) [10]	45	45 [16–59]	GRAAPH 2003	96	NA	53	52 at 48 mo
Fielding (2014) [11]	175	42 [16–64]	UKALLXII/ECOG2993	92	NA	46	38 at 48 mo
Chaladon (2015) [12]	135	49 [18–59]	GRAAPH 2005 Vincristine and dexamethasone	98	29 (2 cycles)	60	48 at 60 mo
	133	45 [21–59]	GRAAPH 2005 hyperCVAD	91	23 (2 cycles)	60	43 at 60 mo
Daver (2015) [13]	54	51 [17–84]	hyperCVAD	93	45 (3 mo)	30	43 at 60 mo
Lim (2015) [14]	87	41 [16–71]	Multiagent chemotherapy	94	66 (at CR)	64	33 at 60 mo
Hatta (2018) [15]	99	45 [15–64]	JALSG ALL202	97	72	60	50 at 60 mo
Dasatinib							
Foa (2011) [23]	53	54 [24–76]	LAL1205 Corticosteroids	93	15 (day 85)	34	69 at 20 mo
Ravandi (2015) [21•]	72	55 [21–80]	Hyper-CVAD	96	65 (3 mo)	17	46 at 60 mo
Chiaretti (2015) [24]	60	42 [19–59]	Corticosteroids ± chemotherapy	97	19 (day 85)	NA	58 at 36 mo
Ravandi (2016) [22]	94	44 [20–60]	Hyper-CVAD	88	NA	44	69 at 36 mo
Rousselot (2016) [25]	71	69 [55–83]	EWALL Vincristine and dexamethasone	96	24	10	36 at 60 mo
Nilotinib							
Kim (2015) [27]	90	47 [17–71]	Multiagent chemotherapy	91	77 (3 mo)	63	72 at 24 mo
Ponatinib							
Jabbour (2015) [35]	64	48 [21–80]	Hyper-CVAD	100	77 (3 mo)	16	76 at 36 mo
Martinelli (2017) [37••]	42	68 [27–85]	Corticosteroids	95	46 (6 mo)	–	87 at 12 mo

Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia; TKI, tyrosine kinase inhibitor; CR, complete remission; CMR, complete molecular remission; AlloHSCT in CR1, allogeneic hematopoietic stem cell transplantation in first remission; OS, overall survival; GMALL, German Multicentric Study Group for Adult ALL; NILG, Northern Italy Leukemia Group; GRAAPH, Group for Research on Adult Acute Lymphoblastic Leukemia; JALSG, Japan Adult Leukemia Study Group; hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; EWALL, European Working Group on adult ALL

Available data confirms the central role of TKIs in the management of patients with Ph+ ALL (Table 1). Currently, the standard of care is combination of a TKI with chemotherapy or corticosteroids. The main remaining question is which TKI is preferable. Due to lack of randomized trials evaluating the superiority of one TKI over the others, statistical efforts have been made to determine the optimal frontline TKI. A matched propensity score analysis identified patients with balanced characteristics treated in two different phase 2 trials with either dasatinib or ponatinib. The combination of hyper-CVAD with ponatinib appeared superior to dasatinib with a 3-year RFS and OS of 69% versus 46%, and 83% versus 56%, respectively [38•]. A meta-analysis combining 25 trials using earlier-generation TKI versus hyper-CVAD and ponatinib also showed higher long-term efficacy of ponatinib. The rate of CMR in pooled analysis using first- or second-generation TKI was 34% compared to 79% with ponatinib. The 3-year OS was significantly higher using ponatinib with 79% compared to 50% with others [39]. In general, the regimen resulting in higher rate of CMR should be selected. Ponatinib is preferred over the others in patients with low risk of cardiovascular complications; otherwise, dasatinib or nilotinib in combination with chemotherapy could be used.

CNS prophylaxis remains a part of the standard of care treatment in patients with ALL. Patients can relapse within the CNS even with dasatinib, known to have a better CNS penetration. In the phase 2 trial of hyper-CVAD and dasatinib, 36% of relapsing patients had CNS-only disease [21•]. We always recommend a total of 12 intrathecal chemoprophylaxis in newly diagnosed patients with Ph+ ALL.

Role of allogeneic hematopoietic stem cell transplantation

In the pre-imatinib era, the prognosis of patients with Ph+ ALL treated with multiagent chemotherapy regimens was dismal. AlloHSCT in first remission was considered standard of care for all patients with an available donor. Patients undergoing alloHSCT lived longer with a 3-year OS of 36% compared to 17% for patients receiving autoHSCT [3]. In the UKALL/ECOG 2993 trial including 267 adult patients with Ph+ ALL, only 28% proceeded to alloHSCT in first remission. The estimated 5-year OS was 44% after matched-related transplant, 36% after matched-unrelated transplant and only 19% after consolidation chemotherapy, confirming the superiority of alloHSCT over chemotherapy [40]. After the breakthrough introduction of TKIs to the backbone chemotherapy with promising long-term outcomes, the usefulness of alloHSCT became questionable. In the GRAAPH-2005 trial, patients with Ph+ ALL were treated with imatinib in combination with steroids or intensive chemotherapy, and those with an available donor proceeded to alloHSCT in first remission. Sixty-three percent of responding patients received alloHSCT, and 14% received autoHSCT. A donor versus no donor analysis did not show a statistically significant difference in outcomes. Furthermore, patients who achieved a major molecular remission (MMR) after the second cycle had similar RFS and OS if they received alloHSCT or autoHSCT [12]. In the nilotinib study by Kim et al., the MRD status after remission was predictive of survival regardless of alloHSCT. Among the patients who achieved CMR, the 2-year molecular RFS was similar between alloHSCT non-recipients and recipients (65% vs 53% respectively, $p = 0.783$). The OS was also similar between the two groups [27].

Clinical outcomes of patients who had alloHSCT in first molecular remission were comparable to those who received autoHSCT with an estimated OS of 70% [41••]. With the emergence of hyper-CVAD and ponatinib as an attractive approach in the frontline treatment of Ph+ ALL, more patients are achieving deep molecular remissions at an early stage. Patients achieving CMR at 3 months had significantly better OS with a 4-year OS rate of 66%, despite not undergoing alloHSCT. CMR at 3 months was the only predictive factor for OS on multivariate analysis and may identify a subgroup of patients with a favorable prognosis, for which the need of alloHSCT in first remission can be obviated [42••].

Blinatumomab

Blinatumomab is a bispecific T cell engager anti-CD3 and CD19 antibody construct, leading to a serial lysis of B cells by redirecting CD3+ T cells toward CD19+ B-ALL cells [43]. Blinatumomab was evaluated in relapsed and/or refractory (R/R) Ph– B-ALL, and has demonstrated superior clinical efficacy as single agent compared to standard chemotherapy. In the TOWER trial, ORR including CR and CRi was achieved in 44% of patients with an estimated median OS of 7.7 months [44–46]. Martinelli et al. recently reported on significant activity of blinatumomab in patients with R/R Ph+ ALL [47••]. In a phase 2 multicentric trial (ALCANTARA), 45 adult patients were treated with blinatumomab after failure of at least one second- or third-generation TKI. The ORR was 36% after 2 cycles of therapy, which was similar to what was reported in the TOWER trial. Among 10 patients with T315I mutation, four achieved CR/CRi; nine had previously received therapy with ponatinib. Among responders, 88% achieved a negative MRD, and 44% had a subsequent alloHSCT. The median RFS and OS were 6.7 and 7.1 months, respectively.

A potential mechanism of resistance to blinatumomab in Ph+ ALL can be the selection of CD19-negative, BCR-ABL1-positive clones [48]. Therefore, the addition of TKI to blinatumomab can potentially overcome this mechanism and can target both CD19- positive and negative clones to prevent relapses. The safety and efficacy of this approach in patients with R/R Ph+ ALL who failed prior TKI were reported by two retrospective studies in a small number of patients [49, 50]. In one study, 12 patients with R/R Ph+ ALL were treated with blinatumomab and TKI (ponatinib, dasatinib, and bosutinib), the ORR (CR/PR) after the first cycle and overall CMR rate were 67% (4/6 patients) and 75% (9/12 patients) respectively. The combination was generally safe with only two reported cases of grade 2 cytokine release syndrome [49]. Another retrospective study on five patients reported same results with CMR achieved in 3 out of 5 patients, MMR in one patient and CCyR in one patient, with no reported related side effects [50]. The combination of blinatumomab with TKI is being further investigated in frontline and R/R setting in ongoing clinical trials. NCT02744768 is a phase 2 trial exploring frontline sequential dasatinib with steroids as induction treatment, followed by blinatumomab infusion in CR. NCT02143414 and NCT03263572 are two ongoing phase 2 trials investigating the combination of blinatumomab with dasatinib and ponatinib, respectively.

Inotuzumab ozogamicin

Inotuzumab ozogamicin is a CD22 monoclonal antibody conjugated to the cytotoxic antibiotic calicheamicin [51]. It was approved by the FDA based on a randomized trial comparing inotuzumab ozogamicin single agent to standard chemotherapy in patients with R/R B-ALL. The CR rate was 81% with an estimated median OS of 7.7 months with inotuzumab treatment [52]. In the phase 1/2 and phase 3 trials evaluating the efficacy of inotuzumab ozogamicin, 38 patients with Ph+ ALL failing prior TKIs were treated [53, 52]. CR/CRi were seen in 9/16 (56%) patients and 16/22 (73%) patients in the phase 1/2 and the phase 3 trials, respectively. The estimated median PFS and OS were 4.4 and 7.4 months in phase 1/2 trial, 3.9 and 8.7 months in phase 3 trial, respectively [54]. Although inotuzumab ozogamicin as single agent is effective in patients with R/R Ph+ ALL, the overall outcomes were still inferior compared to outcomes of patients with Ph– ALL. Thus, combining inotuzumab ozogamicin with TKI can improve responses and ultimately survival rates. In a phase 1/2 trial, 14 R/R Ph+ ALL patients with a median age of 62 years (range, 19–74) were treated with inotuzumab ozogamicin in combination with bosutinib. Patients with T315I mutation were excluded. CR/CRi were achieved in 11 (79%) patients. Among responders, 73% achieved MRD negativity by flow cytometry and 55% achieved CMR. The median EFS and OS were 8.1 and 8.2 months respectively [55]. This trial NCT02311998 is still ongoing and recruiting patients.

Conclusion and future directions

The advent of TKIs in the management of Ph+ ALL has dramatically improved the prognosis of patients. With the use of more potent TKIs like ponatinib in combination with chemotherapy in the frontline setting, the long-term OS is now reaching 80%, compared to as low as 10% in the pre-TKI era. Patients with increased risk of cardiovascular complications may benefit from an alternate TKI such as dasatinib and nilotinib. The achievement of CMR at 3 months regardless of the TKI used is predictive of survival and should be the ultimate goal. Patients achieving early deep molecular remission can potentially continue consolidation and maintenance chemotherapy with TKI without the need for alloHSCT, although this has to be done with detailed discussion of the risks and benefits of either strategy. Patients not achieving this milestone may potentially be treated with blinatumomab to eradicate measurable residual disease and facilitate the transition to alloHSCT. Higher remission rates were also observed with lower-intensity–age-adjusted chemotherapy with a reduced risk of early mortality and acceptable long-term outcomes. This approach is best applicable for older and unfit patients. Combinations of TKIs and antibody-drug conjugates or bispecific monoclonal antibodies, as well as CAR T cells are in development.

Compliance with Ethical Standards

Conflict of Interest

Iman Abou Dalle declares that she has no conflict of interest.

Elias Jabbour has received research funding from Takeda, Pfizer, and Amgen.

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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.

Publisher's Note

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Moorman AV, Harrison CJ, Buck GAN, Richards SM, Secker-Walker LM, Martineau M, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood. 2007;109(8):3189–97. https://doi.org/10.1182/blood-2006-10-051912.
2. Burmeister T, Schwartz S, Bartram CR, Gökbuget N, Hoelzer D, Thiel E. Patients' age and BCR-ABL frequency in adult B-precursor ALL: a retrospective analysis from the GMALL study group. Blood. 2008;112(3):918–9. https://doi.org/10.1182/blood-2008-04-149,286.
3. Thomas X, Boiron J-M, Huguet F, Dombret H, Bradstock K, Vey N, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. J Clin Oncol. 2004;22(20):4075–86. https://doi.org/10.1200/jco.2004.10.050.
4. Kantarjian H, Thomas D, O'Brien S, Cortes J, Giles F, Jeha S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer. 2004;101(12):2788–801. https://doi.org/10.1002/cncr.20668.
5. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med. 1996;2(5):561–6.
6. Platanias LC. Mechanisms of BCR-ABL leukemogenesis and novel targets for the treatment of chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia. Leuk Lymphoma. 2011;52(Suppl 1):2–3. https://doi.org/10.3109/10428194.2010.546922.
7. Ottmann OG, Druker BJ, Sawyers CL, Goldman JM, Reiffers J, Silver RT, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. Blood. 2002;100(6):1965–71. https://doi.org/10.1182/blood-2001-12-0181.
8. Wassmann B, Pfeifer H, Goekbuget N, Beelen DW, Beck J, Stelljes M, et al. Alternating versus concurrent schedules of imatinib and chemotherapy as frontline therapy for Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). Blood. 2006;108(5):1469–77. https://doi.org/10.1182/blood-2005-11-4386.
9. Bassan R, Rossi G, Pogliani EM, Di Bona E, Angelucci E, Cavattoni I, 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. https://doi.org/10.1200/jco.2010.28.1287.
10. Tanguy-Schmidt A, Rousselot P, Chalandon Y, Cayuela JM, Hayette S, Vekemans MC, et al. Long-term follow-up of the imatinib GRAAPH-2003 study in newly diagnosed patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: a GRAALL study. Biol Blood Marrow Transplant. 2013;19(1):150–5. https://doi.org/10.1016/j.bbmt.2012.08.021.
11. Fielding AK, Rowe JM, Buck G, Foroni L, Gerrard G, Litzow MR, 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. https://doi.org/10.1182/blood-2013-09-529008.
12. Chalandon Y, Thomas X, Hayette S, Cayuela JM, Abbal C, Huguet F, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in

adults with Ph-positive acute lymphoblastic leukemia. Blood. 2015;125(24):3711–9. https://doi.org/10.1182/blood-2015-02-627935.

13. Daver N, Thomas D, Ravandi F, Cortes J, Garris R, Jabbour E, et al. Final report of a phase II study of imatinib mesylate with hyper-CVAD for the frontline treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Haematologica. 2015;100(5):653–61. https://doi.org/10.3324/haematol.2014.118588.
14. Lim SN, Joo YD, Lee KH, Kim DY, Lee JH, Lee JH, et al. Long-term follow-up of imatinib plus combination chemotherapy in patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Am J Hematol. 2015;90(11):1013–20. https://doi.org/10.1002/ajh.24137.
15. Hatta Y, Mizuta S, Matsuo K, Ohtake S, Iwanaga M, Sugiura I, 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. https://doi.org/10.1007/s00277-018-3323-8.
16. Shah NP, Tran C, Lee FY, Chen P, Norris D, Sawyers CL. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science (New York, NY). 2004;305(5682):399–401. https://doi.org/10.1126/science.1099480.
17. Tokarski JS, Newitt JA, Chang CY, Cheng JD, Wittekind M, Kiefer SE, et al. The structure of Dasatinib (BMS-354825) bound to activated ABL kinase domain elucidates its inhibitory activity against imatinib-resistant ABL mutants. Cancer Res. 2006;66(11):5790–7. https://doi.org/10.1158/0008-5472.Can-05-4187.
18. Ottmann O, Dombret H, Martinelli G, Simonsson B, Guilhot F, Larson RA, et al. Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase 2 study. Blood. 2007;110(7):2309–15. https://doi.org/10.1182/blood-2007-02-073528.
19. Cortes J, Kim DW, Raffoux E, Martinelli G, Ritchie E, Roy L, et al. Efficacy and safety of dasatinib in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blast phase. Leukemia. 2008;22(12):2176–83. https://doi.org/10.1038/leu.2008.221.
20. Lilly MB, Ottmann OG, Shah NP, Larson RA, Reiffers JJ, Ehninger G, et al. Dasatinib 140 mg once daily versus 70 mg twice daily in patients with Ph-positive acute lymphoblastic leukemia who failed imatinib: results from a phase 3 study. Am J Hematol. 2010;85(3):164–70. https://doi.org/10.1002/ajh.21615.
21.• Ravandi F, O'Brien SM, Cortes JE, Thomas DM, Garris R, Faderl S, 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. https://doi.org/10.1002/cncr.29646
Long term study evaluating the use of hyperCVAD chemotherapy in combination with dasatinib in the frontline treatment of Ph+ ALL.

22. Ravandi F, Othus M, O'Brien SM, Forman SJ, Ha CS, Wong JYC, 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. https://doi.org/10.1182/bloodadvances.2016001495.
23. Foà R, Vitale A, Vignetti M, Meloni G, Guarini A, De Propris MS, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome–positive acute lymphoblastic leukemia. Blood. 2011;118(25):6521–8. https://doi.org/10.1182/blood-2011-05-351403.
24. Chiaretti S, Vitale A, Elia L, Fedullo AL, Albino S, Piciocchi A, et al. Multicenter total therapy Gimema LAL 1509 Protocol for De Novo Adult Ph+ Acute Lymphoblastic Leukemia (ALL) Patients. Updated results and refined genetic-based prognostic stratification. Blood. 2015;126(23):81.
25. Rousselot P, Coude MM, Gokbuget N, Gambacorti Passerini C, Hayette S, Cayuela JM, et al. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. Blood. 2016;128(6):774–82. https://doi.org/10.1182/blood-2016-02-700,153.
26. Weisberg E, Manley P, Mestan J, Cowan-Jacob S, Ray A, Griffin JD. AMN107 (nilotinib): a novel and selective inhibitor of BCR-ABL. Br J Cancer. 2006;94(12):1765–9. https://doi.org/10.1038/sj.bjc.6603170.
27. Kim DY, Joo YD, Lim SN, Kim SD, Lee JH, Lee JH, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Blood. 2015;126(6):746–56. https://doi.org/10.1182/blood-2015-03-636548.
28. Ottmann OG, Pfeifer H, Cayuela J-M, Spiekermann K, Beck J, Jung WE, et al. Nilotinib (Tasigna®) and chemotherapy for first-line treatment in elderly patients with De Novo Philadelphia chromosome/BCR-ABL1 positive acute lymphoblastic leukemia (ALL): a trial of the European Working Group for Adult ALL (EWALL-PH-02). Blood. 2014;124(21):798.
29. Chalandon Y, Rousselot P, Cayuela JM, Thomas X, Clappier E, Havelange V et al. Nilotinib combined with lower-intensity chemotherapy for front-line treatment of younger adults with Ph-positive acute lymphoblastic leukemia (ALL): interim analysis of the GRAAPH-2014 trial. EHA meeting. 2018.
30. Soverini S, De Benedittis C, Papayannidis C, Paolini S, Venturi C, Iacobucci I, et al. Drug resistance and BCR-ABL kinase domain mutations in Philadelphia chromosome-positive acute lymphoblastic leukemia from the imatinib to the second-generation tyrosine kinase inhibitor era: the main changes are in the type of mutations, but not in the frequency of mutation involvement. Cancer. 2014;120(7):1002–9. https://doi.org/10.1002/cncr.28522.

31. Pfeifer H, Wassmann B, Pavlova A, Wunderle L, Oldenburg J, Binckebanck A, et al. Kinase domain mutations of BCR-ABL frequently precede imatinib-based therapy and give rise to relapse in patients with de novo Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). Blood. 2007;110(2):727–34. https://doi.org/10.1182/blood-2006-11-052373.

32. O'Hare T, Shakespeare WC, Zhu X, Eide CA, Rivera VM, Wang F, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell. 2009;16(5):401–12. https://doi.org/10.1016/j.ccr.2009.09.028.

33. Cortes JE, Kim DW, Pinilla-Ibarz J, le Coutre P, Paquette R, Chuah C, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med. 2013;369(19):1783–96. https://doi.org/10.1056/NEJMoa1306494.

34.•• Jabbour E, Kantarjian H, Ravandi F, Thomas D, Huang X, Faderl S, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. Lancet Oncol. 2015;16(15):1547–55. https://doi.org/10.1016/s1470-2045(15)00207-7

Initial results of a phase 2 trial investigating the combination of hyperCVAD chemotherapy in combination with ponatinib in the frontline therapy of Ph+ ALL. This study reported early and deep molecular responses with a 3 year overall survival approching 80%.

35. Short NJ, Kantarjian HM, Ravandi F, Daver NG, Pemmaraju N, Thomas DA, et al. Frontline hyper-CVAD plus ponatinib for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: Updated results of a phase II study. J Clin Oncol. 2017;35(15_suppl):7013. https://doi.org/10.1200/JCO.2017.35.15_suppl.7013.

36. Dorer DJ, Knickerbocker RK, Baccarani M, Cortes JE, Hochhaus A, Talpaz M, et al. Impact of dose intensity of ponatinib on selected adverse events: multivariate analyses from a pooled population of clinical trial patients. Leuk Res. 2016;48:84–91. https://doi.org/10.1016/j.leukres.2016.07.007.

37.•• Martinelli G, Piciocchi A, Papayannidis C, Paolini S, Robustelli V, Soverini S, et al. 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

Initial results of a phase 2 trial by the GIMEMA investigators evaluating the use of ponatinib with corticosteroids in elderly or unfit patients. This study will allow a chemotherapy-free approach for elderly patients who are unfit for intensive chemotherapy.

38.• Sasaki K, Jabbour EJ, Ravandi F, Short NJ, Thomas DA, Garcia-Manero G, et al. Hyper-CVAD plus ponatinib versus hyper-CVAD plus dasatinib as frontline therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: a propensity score analysis. Cancer. 2016;122(23):3650–6. https://doi.org/10.1002/cncr.30231

This study indicates the superiority of hyperCVAD plus ponatinib over dasatinib in the frontline setting using a propensity score analysis.

39. Jabbour E, DerSarkissian M, Duh MS, McCormick N, Cheng WY, McGarry LJ, et al. Efficacy of ponatinib versus earlier generation tyrosine kinase inhibitors for front-line treatment of newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk. 2018;18(4):257–65. https://doi.org/10.1016/j.clml.2018.02.010.

40. Fielding AK, Rowe JM, Richards SM, Buck G, Moorman AV, Durrant IJ, 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. https://doi.org/10.1182/blood-2009-01-199380.

41.•• Giebel S, Labopin M, Potter M, Poire X, Sengeloev H, Socie G, et al. Comparable results of autologous and allogeneic haematopoietic stem cell transplantation for adults with Philadelphia-positive acute lymphoblastic leukaemia in first complete molecular remission: an analysis by the Acute Leukemia Working Party of the EBMT. Eur J Cancer. 2018;96:73–81. https://doi.org/10.1016/j.ejca.2018.03.018

This is a retrospective analysis comparing autologous and allogeneic HSCT in patients with first complete molecular remission in the era of TKIs. Overall survival was comparable between the two groups.

42.•• Short NJ, Jabbour E, Sasaki K, Patel K, O'Brien SM, Cortes JE, et al. Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood. 2016;128(4):504–7. https://doi.org/10.1182/blood-2016-03-707562

Retrospective analysis identifying the achievment of complete molecular remission at 3 months as the only factor predictive of survival with a 4-year overall survival of 66%, without the need for alloHSCT.

43. Zimmerman Z, Maniar T, Nagorsen D. Unleashing the clinical power of T cells: CD19/CD3 bi-specific T cell engager (BiTE(R)) antibody construct blinatumomab as a potential therapy. Int Immunol. 2015;27(1):31–7. https://doi.org/10.1093/intimm/dxu089.

44. Topp MS, Gokbuget N, Zugmaier G, Klappers P, Stelljes M, Neumann S, et al. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. J Clin Oncol Off J Am Soc Clin Oncol. 2014;32(36):4134–40. https://doi.org/10.1200/jco.2014.56.3247.

45. Topp MS, Gokbuget N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, 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. https://doi.org/10.1016/s1470-2045(14)71170-2.
46. Kantarjian H, Stein A, Gokbuget N, Fielding AK, Schuh AC, Ribera JM, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med. 2017;376(9):836–47. https://doi.org/10.1056/NEJMoa1609783.
47.•• Martinelli G, Boissel N, Chevallier P, Ottmann O, Gokbuget N, Topp MS, 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 Off J Am Soc Clin Oncol. 2017;35(16):1795–802. https://doi.org/10.1200/jco.2016.69.3531
Phase 2 trial evaluating blinatumomab in the setting of relapsed/refractory Ph+ ALL with overall response rate of 36%. Blinatumomab was used as a bridge to alloHSCT with acceptable overall survival.
48. Nagel I, Bartels M, Duell J, Oberg HH, Ussat S, Bruckmueller H, et al. Hematopoietic stem cell involvement in BCR-ABL1-positive ALL as a potential mechanism of resistance to blinatumomab therapy. Blood. 2017;130(18):2027–31. https://doi.org/10.1182/blood-2017-05-782,888.
49. Assi R, Kantarjian H, Short NJ, Daver N, Takahashi K, Garcia-Manero G, et al. Safety and efficacy of blinatumomab in combination with a tyrosine kinase inhibitor for the treatment of relapsed Philadelphia chromosome-positive leukemia. Clin Lymphoma Myeloma Leuk. 2017;17(12):897–901. https://doi.org/10.1016/j.clml.2017.08.101.
50. Hanif A, Wang ES, Thompson JE, Baron JI, Walsh MD, Griffiths EA. Combining blinatumomab with targeted therapy for BCR-ABL mutant relapsed/refractory acute lymphoblastic leukemia. Leuk Lymphoma. 2018;59(8):2011–3. https://doi.org/10.1080/10428194.2017.1411595.
51. Yurkiewicz IR, Muffly L, Liedtke M. Inotuzumab ozogamicin: a CD22 mAb-drug conjugate for adult relapsed or refractory B cell precursor acute lymphoblastic leukemia. Drug Des Devel Ther. 2018;12:2293–300. https://doi.org/10.2147/dddt.S150317.
52. Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Stock W, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med. 2016;375(8):740–53. https://doi.org/10.1056/NEJMoa1509277.
53. DeAngelo DJ, Stock W, Stein AS, Shustov A, Liedtke M, Schiffer CA, et al. Inotuzumab ozogamicin in adults with relapsed or refractory CD22-positive acute lymphoblastic leukemia: a phase 1/2 study. Blood Adv. 2017;1(15):1167–80. https://doi.org/10.1182/bloodadvances.2016001925.
54. Stock W, Martinelli G, Stelljes M, DeAngelo DJ, Gökbuget N, Advani AS, et al. Outcomes with inotuzumab ozogamicin (InO) in patients with Philadelphia chromosome–positive (Ph+) relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL). J Clin Oncol. 2018;36(15_suppl):7030. https://doi.org/10.1200/JCO.2018.36.15_suppl.7030.
55. Jain N, Cortes JE, Ravandi F, Konopleva M, Alvarado Y, Kadia T, 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(Suppl 1):143.