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LEUKEMIA (A AGUAYO, SECTION EDITOR)

Philadelphia-Positive Acute Lymphoblastic Leukemia: Current Treatment Options

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Abstract The Philadelphia chromosome (Ph), t(9;22), is seen in about 20 % to 30 % of adults diagnosed with acute lymphoblastic leukemia (ALL). It has been associated with poorer prognosis compared with Ph-negative ALL. Tyrosine kinase inhibitors (TKIs) targeting the *BCR-ABL* oncogenic protein from this translocation have been incorporated into treatment regimens used to treat patients with Ph-positive ALL. Imatinib has been the most widely used TKI with several published trials showing it produced better outcomes when combined with chemotherapy. Dasatinib, a more potent inhibitor than imatinib, has also been evaluated with promising results. However, relapses still occur at a high rate, and allogeneic stem cell transplant is considered, so far, a better curative option in first remission. Additional strategies have also included incorporation of TKIs in the post-transplant setting and the use of newer third generation TKIs. This review provides an update on emerging therapies for adults with Ph-positive ALL.

Keywords Philadelphia chromosome · ALL · Tyrosine kinase inhibitors · Allogeneic stem cell transplant

Introduction

The Philadelphia chromosome (Ph) is the most common cytogenetic abnormality in adult patients with acute lymphoblastic leukemia (ALL), occurring in about 20 % to 30 % of all cases [1–3]. It results from a reciprocal translocation between the *ABL*-1 oncogene on the long arm of chromosome 9 and a breakpoint cluster region (*BCR*) on the long arm of chromosome 22, resulting in a fusion gene, *BCR-ABL*, that encodes an oncogenic protein with constitutively active tyrosine kinase activity [4]. The incidence of Ph-positive ALL increases with age, and occurs in up to 50 % of ALL diagnosed in individuals' ≥50 years old [5, 6]. Patients with Ph-positive ALL have an increased risk for central nervous system (CNS) involvement and an aggressive clinical course. Historically, they had an inferior outcome when compared with their Ph-negative counterparts [7, 8]. This review provides an update of the significant advances in the treatment of Ph-positive ALL in the past few years.

Historical Regimens Prior to the Introduction of Tyrosine Kinase Inhibitors

Prior to the advent of tyrosine kinase inhibitors (TKIs), patients with Ph-positive ALL who were treated with combination chemotherapy regimens were able to achieve complete response (CR) rates of 45 % to 90 %. However, most relapsed, with very few long-term survivors (Table 1). Allogeneic stem cell transplantation (allo SCT) remains the only curative option for patients with suitable matched donors and who are able to tolerate the procedure. However, allo SCT is only available to a limited number of patients, given that a significant proportion of patients with Ph-positive ALL are older. Relapse rates following allo SCT and treatment-related mortality remain high. The United Kingdom Acute Lymphoblastic Leukaemia (UKALL) XII/Eastern Cooperative Oncology Group E2993 trial evaluated the efficacy of allo SCT (in the pre-imatinib era) following

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Table 1 Selected chemotherapy trials in patients with Ph+ ALL [50]

Study	Ph+, N (%)	CR%	Median EFS/CRD (mo)	Median OS (mo)
Bloomfield et al [51]	29 (17)	46	7	11
Gotz et al [52]	25	76	NA	8
Larson et al [53]	30 (27)	70	7	11
GFCH [54]	127 (29)	59	5	NA
Secker-Walker et al [55]	40 (11)	83	13	11
Wetzler et al [1]	67 (29)	79	11	16
Faderl et al [56]	67 (13)	55,90 [a]	8,10.8[a]	11.3, 16.5[a]
Dombret et al [57]	154	67	-	19 % at 3 y[b]
Arico et al [58]	326	82	28 % at 5 y[b]	40 % at 5 y[b]
Schrappe et al [59]	61 (1)	75	38 % at 5 y[b]	49 % at 5 y[b]

GFCH, Groupe Francais de Cytogenetique Hematologique; CR, complete response; EFS, event-free survival; CRD, complete remission duration; OS, overall survival.

[a] Results for the VAD and hyper-CVAD regimens quoted, respectively.

[b] Estimated survival.

achievement of complete hematologic response (CHR) after standard induction combination chemotherapy [9]. Complete remission was achieved in 82 % of the 267 patients with Ph-positive ALL. In patients who underwent allo SCT, the 5-year overall survival (OS), event-free survival (EFS) and relapse-free survival (RFS) rates were significantly better than those who received chemotherapy alone. However, only 28 % of the study patients underwent allo SCT, age older than 55 years and occurrence of pre-allo SCT events being the main reasons for not proceeding with SCT. When patients were matched for age and presenting white blood cell count, and the patients who relapsed before the median time to proceed to transplant were removed, the benefit was limited to event-free survival (EFS) and not overall survival (OS).

Use of Imatinib

With the advent of tyrosine kinase inhibitors (TKIs), there has been improvement in response rates and survival of patients with Ph-positive ALL. It is now standard practice to incorporate TKIs into the frontline regimens for patients with newly diagnosed Ph-positive ALL. In a study by Ottmann and colleagues in patients with relapsed/refractory Ph-positive ALL, imatinib resulted in high response rates, but it was followed quickly by rapid disease progression [10]. Improvement in outcomes has been reported in several studies incorporating imatinib into frontline chemotherapy programs (Table 2).

A major mechanism of secondary resistance to imatinib appears to be related to the acquisition of point mutations within the *BCR-ABL* kinase domain, over 30 of which have been documented [11]. Generally, these mutations fall within one of four regions of the kinase domain: contact site (eg, T315I, F317L), SH2 binding site (eg, M351T), the ATP binding loop (P-loop) (eg, Y253 and E255), and A-loop. The "gatekeeper" contact site mutations (ie, T315I and F317L) prevent binding between imatinib and BCR-ABL, thus, causing resistance to imatinib as well as most second-generation TKIs. Mutations have been reported to be present at time of diagnosis in some patients who are primarily refractory to treatment and in those with relapsed disease [12]. These may contribute to possible subsequent relapse with further therapy, suggesting a potential role for the frontline use of second or third generation TKIs.

Other *BCR-ABL*-independent mechanisms of resistance include decreased drug influx and activation of other downstream or parallel cell signaling pathways that promote cell proliferation and survival, such as the *Src*-family kinases (SFKs) [13, 14].

Second Generation TKIs

Dasatinib

Dasatinib is a dual *BCR-ABL* and *Src* kinase inhibitor with approximately 325-fold greater activity than imatinib against *BCR-ABL*, and with activity against commonly occurring mutations resistant to imatinib, with the exception of T315I [15, 16]. Unlike imatinib, dasatinib is not affected by decrease in activity of the organic cation transporter-1 protein [17]. Furthermore, its activity against Src-family kinases (SFKs)

Table 2 Selected trials of frontline chemotherapy and Imatinib in Ph+ ALL

Study	N	Median age (y)	Median follow-up (mo)	CR (%)	Relapse (%)[a]	OS, %
Delannoy et al [60, 61]	30	66	64	90	15	20 (3-y)
Yanada et al [62]	80	48	13	96	26	76 (1-y)
De Labarthe et al [63]	45	45	NR	96	19	65 (18-mo)
Ribera et al [64]	30	44	49	90	33	30 (4-y)
Bassan et al [65]	59	45	≥36	92	37	38 (5-y predicted)
Pfeifer et al [66, 67]	335	43	NR	88	8.7	40 (4-y)
Fielding et al [9, 68]	175	40	98	82	NR	42 (3-y)
Thomas et al [69, 70]	54	51	77	93	26	54 (3-y)

CR complete response; *OS* overall survival; *NR* not reported.

[a] Denominator used: number of patients achieving CR.

targets bcr- abl-independent pathways [18]. Dasatinib also has been reported to have a higher CNS penetration compared with imatinib [19]. Dasatinib is currently approved by the Food and Drug Administration (FDA) for the treatment of all phases of chronic myeloid leukemia (CML) and for patients with Ph-positive ALL resistant or intolerant to prior therapy, including imatinib [20].

Dasatinib has been incorporated into treatment programs for adults with Ph-positive ALL (Table 3). In a phase 1 dose-escalation study of dasatinib in imatinib-resistant patients 10 patients had Ph-positive ALL: 7 achieved CHR and 8 had major cytogenetic response (MCyR), though responses were short-lived with most relapsing after a median follow-up of 4 months (range, 1-8 months) [21]. The pivotal phase 2 trial which led to the approval of dasatinib for second-line treatment of Ph-positive ALL included 46 patients: 96 % were imatinib-resistant, with BCR-ABL mutations in 78 % (20 % of which were T315I); 37 % of the patients had undergone a prior allo SCT; response rates were high with a rapid time to response (median, 29 days); and with relatively durable response duration (median, 6.3 months) [22, 23]. This was followed by an international randomized phase 3 dose-optimization study comparing 2 different dose schedules of dasatinib [24]. Dasatinib at a dose of 140 mg orally once daily resulted in no significant difference in response and survival rates to dasatinib at a dose of 70 mg orally twice daily, but was associated with a lower incidence of pleural effusion. This led to the change in approved dosing by the FDA to 140 mg once daily orally for this indication.

Investigators at the MD Anderson Cancer Center (MDACC) have reported the results of a phase II study of dasatinib combined with intensive chemotherapy (hyper-CVAD) in patients with relapsed Ph-positive ALL (n=18)

Table 3 Selected phase 2/3 Dasatinib with or without chemotherapy trials

Study	N	Median Age (Y)	Minimum Follow-up (Mo)	CR (%)	CCyR (%)	CMR (%)	Median PFS (Mo)	Median OS (Mo)
Porkka [23]	46	48	24	35	54	NR	3.3	NR
Lilly [24]	44[a]	51	24	25	39	NR	3.1	9.1
	40[b]	51	24	33	50	NR	4.0	6.5
Ravandi [25, 26]	32	49	NR	72	94	47	NR	9.0
Foa [27•, 71]	53	53.6	NR	92.5	NR	52.1	21.5	30.8
Ravandi [28, 29]	61	56	NR	94	NR	NR	NR	NR
	30	71	NR	97	NR	33	NR	NR
Lee [72]	36	47	NR	100	NR	17	NR	NR

CR complete response; CCyR complete cytogenetic response; CMR complete molecular response; PFS progression-free survival; OS overall survival.

[a] Dasatinib dose 70 mg orally twice daily.

[b] Dasatinib dose 140 mg orally once daily.

and blast phase of CML (n=14) [25, 26]. The overall response rate was 94 %. With a median follow up of 27 months, 14 patients were still alive (10 remaining in CR/CR with incomplete platelet recovery). In the frontline setting, the investigators from the GIMEMA LAL1205 trial, reported achievement of CHR in all patients with Ph-positive ALL, irrespective of their age; dasatinib plus steroids was tolerated well, with no induction deaths [27•]. At 20-month follow up, overall survival was 69 % and disease-free survival was 51 %. We have recently reported the results of a trial combining dasatinib and chemotherapy (hyperCVAD) in 35 newly diagnosed patients with Ph-positive ALL with 94 % complete remission rate and estimated 2-year survival of 64 % [28, 29]. In another recent report in older patients (age >55 years), Rousselot and colleagues used induction treatment with steroids, vincristine and dasatinib in elderly patients with Ph-positive ALL, followed by consolidation cycles of dasatinib, and chemotherapy, resulting in 97 % CR rate and 33 % complete molecular response (CMR) rate [30]. With a median follow-up of 12.4 months, median EFS and OS were not reached..

Nilotinib

Is an orally active derivative of imatinib with an increased and more selective binding affinity to the ATP pocket of BCR-ABL oncoprotein, resulting in 20 - 50 times higher than the inhibitory activity of imatinib [31]. Kantarjian et al first reported the phase 1 dose-escalation study of nilotinib in imatinib-resistant CML or Ph-positive ALL, which included 33 patients with blast phase. Overall, 13 patients (39 %) achieved a hematologic response and 9 (27 %) had a cytogenetic response (including 6 with major cytogenetic response) [31]. One of 10 patients with Ph-positive ALL in hematologic relapse had a partial response, and 1 of 3 patients with Ph-positive ALL with persistent molecular positivity achieved CMR. Nilotinib demonstrated activity against most kinase domain mutations, with the exception of T315I and P-loop mutations. It is currently approved for use in the treatment of newly diagnosed patients with CML and patients with chronic phase CML who are resistant to or are intolerant of imatinib. Nilotinib is not approved for use in patients with Ph-positive ALL [32]. Kim et al reported the use of nilotinib in combination with chemotherapy for frontline treatment of patients with newly diagnosed Ph-positive ALL, with 90 % hematologic remission rate and 54 % complete molecular remission rate. With a median follow-up of 17.4 months, the estimated relapse-free survival and overall survival at 2 years were 71 % and 66 %, respectively [33]. In another recently reported study, the use of nilotinib in myeloid (MBP, n=105) or lymphoid blast phase (LBP, n=31) of CML was evaluated. After a minimum follow-up of 24 months on nilotinib 400 mg orally twice daily, major hematologic responses were seen in 60 % of patients with MBP and 59 % of patients with LBP. Complete cytogenetic response was achieved in 30 % of patients with MBP and 32 % of patients with LBP. Median overall survival was 10.1 months for patients with myeloid blastic phase and 7.9 months for patients with lymphoid blastic phase [34].

Other Agents

Bosutinib (formerly, SKI-606) is another dual *Src* and *Abl* tyrosine kinase inhibitor with demonstrated significant activity in patients with Ph+ leukemias with resistance or intolerance to imatinib across all baseline BCR-ABL kinase domain mutations, except most notably for T315I. In a report of activity of this drug by mutational status by Gambacorti-Passerini et al, when patients were grouped as to the presence or absence of mutations, not including T315I, CHR was 78 % and MCyR was 56 % for those with mutations, compared with 82 % and 53 %, for those without mutations [35].

Ponatinib (formerly, AP24534) is a pan-inhibitor of *BCR-ABL* and its mutants, including those with the resistant T315I mutation. Among the 403 patients included in the pivotal phase 2 trial, 94 patients had CML lymphoid blast phase or Ph+ ALL, and were resistant or intolerant to other TKIs [36]. With a short median follow up of 2 months, the major hematologic response were noted to be 37 % and 27 %, in patients with resistance/intolerance to prior TKI and those with T315I mutation, respectively. With the use of dasatinib in the frontline setting, most relapses were associated with T315I mutation; hence, ponatinib combined with chemotherapy is a promising approach [27•].

DCC-2036 is a potent and novel TKI which binds to the "switch pocket", thereby preventing the BCR-ABL from conforming into an active state. In the recent report of the phase 1 trial of DCC-2036, 30 patients including 19 patients with CML-chronic phase, 8 patients with CML-accelerated phase and 3 with CML-blast phase were treated [37]. Preliminary responses include: 1 MMR, 1 CCyR, and 1 partial cytogenetic response in patients with chronic phase disease; 1 CHR and 1 partial hematologic response in CML-accelerated phase patients.

Allogeneic Stem Cell Transplant (ALLOSCT)

Allo SCT is still considered as the best treatment option for patients with Ph-positive ALL in first CR, although long-term results of regimens combining chemotherapy with TKIs suggest the possibility of long-term survival in a proportion of patients who do not undergo allo SCT.

Transplant has significant treatment-related morbidity and mortality, and is not always possible [19]. Age is a very important predictor of poor outcome with allo SCT [38]. Reduced-intensity conditioning regimens are under evaluation and have reported acceptable results with lower treatment related mortality rates [39–42]. Outcome of SCT depends most significantly on disease status at the time of transplantation, with dismal results expected with larger disease burden. In patients with suitable donors, the introduction of TKIs has increased the likelihood of patients proceeding to transplantation, as shown by the UKALL-XII/ECOG2993 trial, where 44 % of patients receiving imatinib in any form/dose/schedule were able to proceed to alloSCT compared with 28 % in the pre-imatinib era [38] Therefore, TKIs produce significant and durable responses, most notably dasatinib and nilotinib [21, 31]. They allow for allo SCT to proceed in patients with CML or Ph-positive ALL with less disease burden, and do not increase SCT-related toxicities [43].

With improvement of results seen with the incorporation of TKIs to frontline regimens of Ph-positive ALL, the role of allo SCT in first remission is being debated. In the study of the Children's Oncology Group, Schulz et al found that intensive chemotherapy plus imatinib improved 3 year EFS for children and adolescents, with minimal toxicities, compared with historical controls (pre-imatinib era) [44••]. In addition, 3 year EFS was similar for the cohort of pts treated with chemotherapy and imatinib at 88 %±11 % compared with sibling donor SCT at 57 %±22 %. There was no suggestion that outcomes were superior with allo SCT compared with intensive chemotherapy plus imatinib.

In an earlier report, Carpenter et al showed that imatinib could be safely administered early after myeloablative allo SCT [45]. More recently, Pfeifer et al reported long term results of their randomized comparison of prophylactic versus pre-emptive use of imatinib following allo SCT, which showed that imatinib significantly reduced the incidence of molecular relapse [46]. In addition, the use of imatinib both prophylactically and pre-emptively were associated with low rates of hematologic relapse, durable remissions and excellent long term outcomes in Ph-positive ALL.

Monitoring of Minimal Residual Disease (MRD)

We have recently reported that achievement of a negative MRD status by multiparameter flow cytometry can be associated with a significant improvement of survival, and patients with persistent MRD may benefit from intensification of treatment with an alloSCT in first CR [47]. In addition, MRD has been shown to predict for disease relapse post allogeneic SCT [48]. For patients with Ph-positive ALL, monitoring of *BCR-ABL* transcripts may be performed using reverse transcription polymerase chain reaction (RT-PCR). However, unlike in CML, there are generally no accepted definitions of molecular responses in Ph-positive ALL that could serve as the basis for therapeutic decisions. In a study initiated by the EWALL and ESG-MRD-ALL consortia, involving 30 laboratories from 14 countries worldwide, Pfeifer et al noted a high variability in RNA yield between the different laboratories despite using the same PCR techniques, leading to up to 3-log difference in ABL copy numbers [49].

Conclusions

The TKIs have significantly improved outcomes for adult patients with Ph-positive ALL, with the use of imatinib in combination with intensive chemotherapy early in the treatment course, and continuing through consolidation and maintenance considered as the current standard of care. Allo SCT in first CR should still be considered for patients with a suitable donor who are able to tolerate the procedure. The second-generation TKIs, such as dasatinib, are likely to yield better results and ongoing trials are evaluating them in combination with chemotherapy. Monotherapy with TKIs should be reserved for the elderly and those unable to tolerate intensive chemotherapy. Monitoring MRD should be part of standard care of all patients with Ph-positive leukemias. Although high initial response rates are seen with the incorporation of TKIs, disease relapse remains a major cause of mortality. There is further need for incorporating newer agents, like ponatinib, which overcomes resistance related to the T315I mutation, a frequent cause of Ph-positive ALL resistance, to potentially achieve more durable responses.

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- •• Of major importance

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