The Emerging Use of Chemotherapy-Free Regimens in Adults With Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia

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Abstract: Before the development of tyrosine kinase inhibitors (TKIs), the outcome of patients with a diagnosis of Philadelphia chromosome (Ph)–positive acute lymphoblastic leukemia was dismal. Combinations of TKIs and chemotherapy improved survival rates, but allogeneic stem cell transplant was still relied on to avoid relapse in most cases. More recently, the chemotherapy-free combination of blinatumomab plus newer-generation TKIs has shown favorable results and may eliminate the need for allogeneic stem cell transplant. This review discusses the evolution of the treatment of Ph-positive acute lymphoblastic leukemia with chemotherapy-free regimens in the current era.

Keywords
BCR-ABL1, blinatumomab, ponatinib, tyrosine kinase inhibitor

Introduction

Philadelphia chromosome (Ph)–positive acute lymphoblastic leukemia (ALL) is characterized by the *BCR-ABL1* fusion, which is present in approximately 25% to 30% of cases of B-cell ALL. This abnormality historically carried a poor prognosis until BCR-ABL1 tyrosine kinase inhibitors (TKIs) became available. The 5-year survival rate increased from 20% with chemotherapy alone to 50% with the combination of a first- or second-generation TKI and conventional chemotherapy and to up to 75% with the third-generation TKI ponatinib (Iclusig, Ariad Pharmaceuticals).[1-6]

Despite these improvements, allogeneic hematopoietic stem cell transplant (allo-SCT) offered the best chance for cure. After the achievement of first complete remission, allo-SCT was generally recommended for fit patients. However, intensive induction

chemotherapy and allo-SCT are not viable options for all patients because of the high risk of mortality, especially in older adults. This review highlights the progress accomplished in the treatment of Ph-positive ALL, including the use of novel, chemotherapy-free TKI- and blinatumomab-based regimens that are eliminating the need for allo-SCT in this population.[7]

First-Generation TKIs

A major paradigm shift in the therapy for Ph-positive ALL occurred with the discovery of targeted TKIs. TKIs have the unique ability to target and inhibit the autophosphorylation caused by the BCR-ABL1 kinase protein.[8] The use of imatinib as monotherapy in Ph-positive ALL was established in the early 2000s, and imatinib was subsequently used in combination with chemotherapy; however, this treatment strategy still relied heavily on allo-SCT for long-term disease control.[9]

The UKALL XII/ECOG E2993 trial compared the outcomes of patients who had newly diagnosed Ph-positive ALL treated with imatinib plus chemotherapy (early imatinib n=89, late imatinib n=86) vs the outcomes of patients managed with historical pre-imatinib therapy (n=266). The overall complete response (CR) rate was 92% the imatinib group vs 82% in the pre-imatinib group (*P*=.004). The patients who received imatinib at any time had better 4-year overall survival (OS; 38% vs 22%), relapse-free survival (RFS; 50% vs 33%), and event-free survival (EFS; 33% vs 18%) in comparison with the patients in the pre-imatinib era; earlier exposure to imatinib also improved outcomes. Of the 175 included patients, 98 (56%) proceeded to allo-SCT. OS was better in the patients who were able to proceed to allo-SCT than in those who received chemotherapy alone. Therefore, these findings suggested that the addition of imatinib early during induction improved response rates and allowed more patients to proceed to allo-SCT, which likely drove the improved survival outcomes.[5] Importantly, this study was among the first to show a benefit of allo-SCT for Ph-positive ALL, even in the TKI era (see Table for a summary of treatment studies).

In 2006, Thomas and colleagues published results of a study of the combination of imatinib plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD), alternating with high-dose cytarabine and methotrexate, in patients with newly diagnosed or refractory Ph-positive ALL. Of the 43 evaluable patients, 93% achieved a CR; the complete molecular response (CMR) rate in those not receiving a transplant was 58% (in 33 evaluable patients). Additionally, all patients with relapse at study initiation achieved a CR. At a median follow-up of 4 years, the 5-year OS rate was 43%. Outcomes favored the imatinib combination in comparison with hyper-CVAD alone. The 3-year disease-free survival (DFS) rate was 62% with the combination vs 14% without imatinib, and the 3-year OS rates were 55% and 15%, respectively (*P*<.001). Of the 43 patients, 30% underwent allo-SCT, yet no difference in OS was observed when they were compared with those who did not undergo allo-SCT. However, a longer CR was noted in those who received allo-SCT if persistent disease was still present at completion of therapy.[3,10,11]

Similar outcomes were seen in a randomized trial of 268 patients with Ph-positive ALL that compared high doses of imatinib combined with reduced-intensity chemotherapy (vincristine plus corticosteroids) vs standard-dose imatinib combined with high-intensity chemotherapy (hyper-CVAD). Planned allo-SCT was performed if a major molecular response was achieved after cycle 2. EFS and OS rates at 5 years were 37.1% and 45.6%, respectively, for the entire study population, without any difference between the arms. Transplant was performed in 161 patients (60%) in first complete remission, and 38 patients received post-transplant TKI therapy. Although transplant was associated with prolonged RFS and OS, the non–relapse-related mortality rate was as high as 25%, even in those who received reduced-intensity conditioning regimens.[12] These data suggest that the combination of imatinib plus chemotherapy followed by allo-SCT may improve outcomes, but at the potential cost of transplant-related mortality.

Second-Generation TKIs

Molecular responses in patients with Ph-positive ALL were more rapid when second-generation TKIs were combined with chemotherapy than when the first-generation TKI imatinib was used. In a study of 186 pediatric patients, EFS and OS were improved and risk of relapse was lower in a comparison of dasatinib (Sprycel, Bristol Myers Squibb) combined with chemotherapy vs imatinib.[13] This study provides strong data supporting the use of a second-generation TKI (rather than imatinib) in patients with Ph-positive ALL. Unfortunately, robust randomized data comparing different TKI combinations are not yet available in the adult population.

Hyper-CVAD plus dasatinib has been evaluated in patients with newly diagnosed or relapsed Ph-positive ALL. In a single-institution phase 2 study of this combination, 72 patients were treated (median age, 55 years); 96% of them achieved a CR, and 83% achieved a cytogenetic CR after the first cycle. After a median of 4 weeks, 93% had achieved a major molecular response. Of the patients with relapse, 7 had detectable *ABL1* kinase

Table. Summary of Treatment Studies in Ph-Positive Acute Lymphoblastic Leukemia

Trials (Year)	Population	N	Median Age, y (Range)	CR/CRi, %	CMR, %	Allo-SCT, n	OS Rate, %
Imatinib							
Vincristine/dexamethasone vs hyper-CVAD (2015)[12]	ND	135 133	49 (18-59) 45 (21-59)	98 91	23 28	91 97	*At 5 y (both arms)* 46
UKALL XII/ECOG E2993 (2014)[5]	ND	175	42 (16-64)	92	NA	98	*At 4 y* 38
Hyper-CVAD (2015)[3]	ND	54	51 (17-84)	93	45	16	*At 5 y* 43
Vincristine/daunorubicin/ corticosteroids (2015)[54]	ND	87	41 (16-71)	94.3	89	56	*At 5 y* 33
Nilotinib							
Vincristine/dexamethasone (2014)[9]	ND	79	65 (55-85)	94	58	24	*At 4 y* 47
Vincristine/daunorubicin/ corticosteroids (2015)[20]	ND	90	47 (17-71)	91	94	57	*At 2 y* 72
Vincristine/dexamethasone (2021)[7]	ND	156	47 (18-60)	97	NA	132	*At 3 y* 74
Dasatinib							
Vincristine/dexamethasone (2016)[16]	ND	71	69 (59-83)	96	24	7	*At 3 y* 33
Hyper-CVAD (2015)[14]	ND	72	55 (21-80)	96	60	12	*At 5 y* 50
Blinatumomab (2022)[32]	ND	63	54 (24-82)	98	41	29	At 2 *y* 88
Ponatinib							
Corticosteroids (2022)[22]	ND	44	66 (26-85)	96	40.9	NA	NR[a]
Hyper-CVAD (2019)[26]	ND	86	46 (21-80)	100	84	18	*At 5 y* 73
Blinatumomab (2022)[33,36]	ND R/R CML-LBP	40 14 6	57 (38-83) 38 (32-61) 69 (57-76)	96 92 83	87 79 33	1 6 NA	*At 2 y* 93 61 60

[a]20 patients (45.5%) deceased at time of analysis.

allo-SCT, allogeneic hematopoietic stem cell transplant; CML-LBP, chronic myeloid leukemia in lymphoid blast phase; CMR, complete molecular response; CR, complete response; CRi, CR with incomplete count recovery; hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; N, number of patients; NA, not applicable; ND, newly diagnosed; NR, not reached; OS, overall survival; R/R, relapsed/refractory; y, years.

domain mutations, 4 of which were the T315I mutation. Twelve patients (16%) in first complete remission received allo-SCT.[14] The median DFS was 31 months, and OS was 47 months. In a similar multicenter study of 97 patients with newly diagnosed Ph-positive ALL, the same regimen of hyper-CVAD plus dasatinib was used, with plans for all eligible patients to undergo allo-SCT in first complete remission. Although this study showed that survival was improved in the patients who received allo-SCT, only 43% of the patients were able to proceed to allo-SCT upon completion of chemotherapy.[15]

Because of the need for less-intensive yet effective regimens for older patients, in whom allo-SCT is not suitable, Rousselot and colleagues evaluated lower-intensity chemotherapy plus dasatinib. Among the 71 patients (median age, 69 years) analyzed, the CR rate was 96%, the CMR rate was 24%, and the 5-year OS rate was 45% (excluding non–leukemia-related deaths). It should be noted that of the 36 patients with relapse, 75% had a T315I mutation, and relapses occurred earlier in the

patients who acquired this mutation.[16] Additional studies have confirmed the efficacy of dasatinib, but acquisition of the T315I mutation remains the dominant mechanism of disease relapse in patients treated with first- or second-generation TKIs.[17]

Other second-generation TKIs have achieved promising outcomes in older patients with Ph-positive ALL. Nilotinib (Tasigna, Novartis) in combination with reduced doses of hyper-CVAD was evaluated in EWALL-PH-02 from the European Working Group for Adult ALL and resulted in a CMR rate of 58%.[18,19] In addition, CMR rates of 94% were seen with nilotinib in patients receiving concurrent vincristine, prednisolone, and daunorubicin.[20] However, as in the EWALL study, acquisition of the T315I kinase domain mutation was common at the time of relapse.

Third-Generation TKI

Because of the dominant role of T315I mutations in causing relapse, TKIs with activity against this common resistance mutation are needed.[21] Ponatinib is a pan–BCR-ABL1 inhibitor that is active against different *ABL1* kinase domain mutations, including T315I mutations.[12] Given the broad spectrum of activity of ponatinib, several investigators have evaluated it in the frontline setting in an attempt to prevent the development of T315I (and other) resistance mutations.

In a phase 2 study of patients with newly diagnosed disease who were unfit for intensive chemotherapy, those aged 60 years and older were treated with a combination of ponatinib and corticosteroids; prophylactic intrathecal chemotherapy was also administered monthly. Ponatinib was given at a dose of 45 mg daily for 48 weeks, and prednisone was given at a dose of 60 mg/m^2 daily and then tapered from days 14 to 29. In the 44 evaluable patients, whose median age was 66 years, the CMR rate at 24 weeks was 40.9%, and the overall CMR rate at any time point was 81.8%. Despite the target dose of 45 mg, the median daily dose of ponatinib was 29 mg.[22]

The benefit of ponatinib was considerably increased when it was combined with more substantial therapy in more fit patient populations. In the PONALFIL trial, ponatinib was combined with intensive chemotherapy followed by allo-SCT in patients with newly diagnosed Ph-positive ALL. Ponatinib was also continued following transplant in patients with persistence of measurable residual disease (MRD) or recurrence. The median age of the study population was 49 years. A CR was attained in all 30 patients, and a CMR was achieved in 20 patients (71%) after consolidation. Of note, of the patients without a CMR after consolidation, 4 showed deletion of Ikaros family zinc finger 1 (*IKZF1*), 2 of them with *IKZF1*^{plus}.[23] A total of 26 patients (93%) received an allo-SCT. This regimen resulted in 3-year EFS and OS rates of 70% and 97%, respectively. Thus, very high rates of long-term survival can be achieved with a combination of chemotherapy plus ponatinib followed by allo-SCT.

The utility of frontline ponatinib was also shown in a phase 2 study of hyper-CVAD plus ponatinib conducted by Jabbour and colleagues. Ponatinib initially was given at a dose of 45 mg daily. However, after 2 fatal cardiovascular events occurred, the protocol was amended to reduce the ponatinib dose to 30 mg daily once a CR was achieved, and further to 15 mg daily once a CMR was achieved; these modifications were associated with reduced ponatinib-related toxicity. A total of 86 patients with a median age of 46 years were treated. The CR rate was 100%, the CMR rate was 84%, and the 5-year OS rate was 73%. Of 11 patients with relapse, only 3 were still on ponatinib at the time of relapse. In a 6-month landmark analysis to assess the role of allo-SCT, the 5-year OS rate was superior in the patients who did not receive an allo-SCT (83% vs 66%; P=.07).[24-26] These results suggest that many patients may be spared allo-SCT when a ponatinib-based regimen is used, particularly those with a CMR.

Blinatumomab and TKI Regimens

Blinatumomab (Blincyto, Amgen) is a CD3-CD19 bispecific T cell–engaging antibody that is approved as a single agent for patients with relapsed/refractory B-cell ALL and for those with MRD-positive B-cell ALL. Blinatumomab as monotherapy is active in patients with Ph-positive ALL, including those with prior allo-SCT and/or ponatinib exposure.[27] Retrospective studies have also showed the activity of blinatumomab in combination with a TKI in patients with relapsed/refractory Ph-positive ALL. For example, Assi and colleagues retrospectively reported on 12 patients with heavily pretreated Ph-positive ALL and chronic myeloid leukemia in lymphoid blast phase (CML-LBP)—including some with prior allo-SCT—who received a combination of blinatumomab and a TKI (ponatinib, n=8; dasatinib, n=3; bosutinib [Bosulif, Pfizer], n=1). With a median follow-up of 8 months, the CMR rate was 75% (9 of 12), and the 1-year overall survival rate was 73%.[28] Similar outcomes were reported in a retrospective analysis of 26 patients with relapsed-refractory disease treated with a combination of ponatinib and blinatumomab, in which all patients showed a response to therapy; 23 of the 26 patients achieved a CMR.[29] On the basis of these results, combination therapy with a TKI and blinatumomab was investigated in the frontline setting.

The landmark D-ALBA trial analyzed combination

therapy with blinatumomab and dasatinib in patients with newly diagnosed Ph-positive ALL. The study recruited 63 patients of all ages (≤85 years), who received corticosteroids plus dasatinib at 140 mg daily for 85 days. The patients then received consolidation with blinatumomab for up to 5 cycles in combination with dasatinib. The deep molecular response rate (CMR plus positive nonquantifiable response) increased from 29% with corticosteroids and dasatinib alone to 60% after the addition of 2 cycles of blinatumomab. At the completion of 5 cycles of the dasatinib/blinatumomab combination, the deep molecular response rate was 72%.[30] Long-term results of this trial showed an OS rate of 78% at 40 months. A total of 9 relapses were noted—4 within the central nervous system, 4 hematologic, and 1 nodal—with a median time to relapse of 4.4 months (range, 1.9-25.8 months). Of the 58 patients who started blinatumomab, 29 (50%) subsequently received allo-SCT, generally after 2 to 3 cycles of blinatumomab. Allo-SCT did not affect OS or DFS, although the patients with persistent molecular disease were preferentially recommended to receive allo-SCT, which may have skewed the results.[30-32] This study prospectively showed that a chemotherapy-free approach with blinatumomab plus a TKI is safe and feasible in patients of all ages with newly diagnosed Ph-positive ALL.

The combination of ponatinib/blinatumomab was evaluated in a phase 2 trial of patients with newly diagnosed or relapsed/refractory Ph-positive ALL. Ponatinib was administered continuously at a dose of 30 mg, then reduced to 15 mg once a CMR was obtained. The patients received 5 cycles of blinatumomab overall. Unlike in the D-ALBA study, blinatumomab was introduced in cycle 1. All patients received 12 doses of prophylactic intrathecal chemotherapy. In the most recent update, 40 patients with newly diagnosed Ph-positive ALL whose median age is 57 years have been treated, with a CR rate of 96%. A total of 68% of patients undergoing frontline treatment achieved a CMR after 1 cycle, and 87% achieved a CMR at any time point. One patient underwent allo-SCT because of persistently detectable *BCR/ABL1* transcripts. At a median follow-up of 15 months, no relapse has occurred in the cohort with newly diagnosed disease, and the estimated 2-year OS rate for these patients is 95%.[33-36] The promising results of concurrent ponatinib/blinatumomab may offer all patients the opportunity to avoid the morbidity and mortality related to allo-SCT, but longer-term data are needed.

Limited Role of Transplant

Given the advances in chemotherapy-free regimens and the addition of the third-generation TKI, the referral to transplant should be based on an individualized approach. Individuals who fail to achieve CMR at 3 months, have the *IKZF1*^{plus} genotype, or have CML-LBP may require allo-SCT.[37,38]

CMR at 3 Months

Patients who fail to achieve CMR at 3 months have high-risk Ph-positive ALL. In an analysis of 85 patients with Ph-positive ALL who received hyper-CVAD plus a TKI without subsequent allo-SCT, the achievement of CMR at 3 months was highly prognostic for RFS (P=.002) and OS (P=.005).[40] In a multivariate analysis, CMR at 3 months was the only factor associated with a survival benefit.[38,39] Additionally, a retrospective study by Sasaki and colleagues analyzed 204 patients who received a TKI with hyper-CVAD. Overall, a 3-month CMR was obtained in 57% of the patients, including 32% with imatinib, 52% with dasatinib, and 74% with ponatinib. In this analysis, allo-SCT did not improve outcomes in the patients who achieved CMR at 3 months. Among the patients who achieved CMR at 3 months, treatment with ponatinib was the variable that predicted disease progression (P=.028) or death (P=.042).[27,40-42] The role of allo-SCT in patients with Ph-positive ALL who achieve CMR within 3 months appears to be minimal, but randomized clinical trials are needed to confirm. Additionally, among those who do not achieve CMR, blinatumomab can be used to eradicate MRD (along with continuation of a potent TKI, preferably ponatinib), and allo-SCT may still be avoided for many of these patients.

IKZF1^{plus} *Genotype*

Alterations in *IKZF1*, specifically *IKZF1* deletions, occur in approximately 60% of patients with Ph-positive ALL, and some studies have suggested that these alterations may increase the risk of disease relapse.[43] In particular, the "*IKZF1*^{plus}" genotype (generally defined as the presence of an *IKZF1* deletion in combination with a deletion in *CDKN2A/B* and/or *PAX5*) has been linked to a subset of patients with very high-risk Ph-positive ALL whose DFS and OS are significantly shorter than those of patients who do not have *IKZF1* deletions or who have an *IKZF1* deletion only. In both univariate and multivariate analyses, the GIMEMA LAL1509 trial from Italy showed that an *IKZF1*^{plus} genotype was the only factor that affected OS and DFS in patients receiving a dasatinib/corticosteroid combination.[44] Similarly, in the D-ALBA trial, DFS at 30 months was worse in patients with the *IKZF1*^{plus} genotype (41%) than in those without an *IKZF1* deletion (79%) or with an *IKZF1* deletion but no other recurrent genomic abnormalities (55%). The presence of the *IKZF1*^{plus} genotype was also associated with inferior OS.[31]

One retrospective study suggests that ponatinib may overcome the poor prognostic effect of the *IKZF1*^{plus} genotype when earlier-generation TKIs are used. Sasaki and colleagues found that outcomes were improved when ponatinib rather than dasatinib was used in patients with the *IKZF1*^{plus} genotype. Although the response of these patients to therapy remained lower than the response of those who did not have the *IKZF1*^{plus} genotype, the 5-year OS rate was 62% in the patients who received hyper-CVAD plus ponatinib vs 44% in those who received dasatinib plus hyper-CVAD.[15,45] Additionally, in the ongoing trial evaluating frontline blinatumomab and ponatinib, no relapses have been observed among 40 patients being treated de novo.[36] Although comprehensive genomic profiling has not yet been reported for this cohort, the lack of relapses suggests that ponatinib in combination with blinatumomab may overcome the negative prognostic effect of these genomic changes.[33]

Chronic Myeloid Leukemia in Lymphoid Blast Phase

In rare cases, CML may transform to an aggressive lymphoid blast phase that sometimes can be difficult to distinguish from Ph-positive ALL arising de novo. CML-LBP confers inferior outcomes even with the use of TKIs, and it is vital to distinguish CML-LBP from Ph-positive ALL arising de novo when possible. In a retrospective analysis of 275 patients, the common distinguishing features of those with CML-LBP were higher leukocyte and absolute neutrophil counts, higher levels of immature myeloid cells in peripheral blood, lower blast counts, and older age in comparison with their ALL counterparts. Additionally, a subset of 28 patients harbored at least one feature: a large discrepancy between blast count and Ph-positive clone, persistence of Ph-positive clone during remission, and/or detection of *BCR/ABL1* fusion in segmented cells; these features were more common in those harboring p210 transcripts.[46-48]

Hyper-CVAD plus dasatinib was evaluated in 23 patients with CML-LBP (96% with p210 transcripts); 17 of these patients had received a prior TKI (9 imatinib, 6 nilotinib, 1 imatinib and nilotinib, and 1 imatinib and bosutinib). The 5-year OS rate in the patients who had Ph-positive ALL treated with the same regimen was similar to the OS rate in the patients with CML-LBP and Ph-positive ALL (59% vs 48%, respectively). Allo-SCT improved outcomes for patients with CML-LBP (in whom the 5-year OS rate among the patients who received a transplant was 88%) but not for those with Ph-positive ALL.[49] Molecular response rates also were lower in the patients with CML-LBP. On the basis of this analysis, allo-SCT transplant should be strongly considered for patients with CML-LBP, particularly those whose disease has progressed on prior TKI therapy.[50-53]

Summary

With the development of TKI-plus-blinatumomab combinations, most patients with Ph-positive ALL may be able to avoid allo-SCT and chemotherapy, both of which can contribute to significant morbidity and mortality. Treatment with the combination of ponatinib and blinatumomab has shown remarkable responses across all age groups, including older patients. With a longer-term follow-up, this chemotherapy-free combination may become the new standard of care for most patients with Ph-positive ALL and may help to turn Ph-positive ALL from one of the deadliest forms of leukemia into one of the most curable.

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