Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

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KEYWORDS

- Acute lymphoblastic leukemia • Philadelphia chromosome
- BCR-ABL • Tyrosine kinase inhibition
- Allogeneic stem cell transplant

BIOLOGY

The Philadelphia (Ph) chromosome, a short chromosome 22, results from the reciprocal translocation between chromosomes 9 and 22 that fuses the breakpoint cluster region (*BCR*) gene on chromosome 22 to the Ableson (*ABL)* gene on chromosome 9.[1,2] The protein product of the fusion gene, BCR-ABL, has enhanced tyrosine kinase activity leading to the constitutive activation of several downstream pro-proliferative and pro-survival signaling pathways, and hence to leukemogenesis.[3] The Ph chromosome is the most frequent cytogenetic abnormality in adult patients with acute lymphoblastic leukemia (ALL), occurring in approximately 20% to 30% of adults but only in about 5% of children with this disease.[4] The incidence rises with age, and it occurs in approximately 50% of patients older than 50 years.[5]

Depending on the location of the breakpoint within the BCR gene, two major varieties of the oncogenic protein of differing sizes have been recognized. The smaller $P190^{bcr\text{-}abl}$ protein is found in over two-thirds of patients with Ph+ ALL and the larger $p210^{bcr\text{-}abl}$ protein, which is typical of chronic myeloid leukemia (CML) but is also encountered in about one-third of Ph+ ALL patients.[6] In experimental models, the $p190^{bcr\text{-}abl}$ protein has a higher tyrosine kinase activity and is more efficient in stimulating the growth of lymphoid cells.[6,7] However, using traditional chemotherapy regimens, clinical outcomes in patients carrying either of the two proteins have been generally similar.[6,8]

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TREATMENT OF ADULTS AND CHILDREN WITH PH+ ACUTE LYMPHOBLASTIC LEUKEMIA

Historical Perspectives

Before the introduction of imatinib, the outcome of patients with Ph+ ALL was poor. Although complete remission (CR) could be achieved in the majority of patients (60%–90%), the median CR duration was considerably shorter than that seen in patients with Ph-negative disease, leading to very few long-term survivors (**Table 1**). This discrepancy was to some degree age dependent, with better survival reported in children with Ph+ ALL, particularly for those with a good initial response to glucocorticoid therapy.[9,10] On the other end of the age spectrum, specifically those older than 50 to 60 years, the outcome was particularly dismal with high treatment-related mortality, low CR rates, and short disease-free survival (DFS) and overall survival (OS).[5,11,12]

The relatively uniform dismal prognosis in adult patients with Ph+ ALL using conventional chemotherapy regimens meant that few predictors of outcome had been identified. However, it is notable that even with such suboptimal regimens, the degree of reduction of *BCR-ABL* transcripts after induction and consolidation was found to be a powerful predictor of disease response and survival.[13] This finding may indicate the potential role for monitoring *BCR-ABL* transcript levels when using regimens containing tyrosine kinase inhibitors (TKIs).

Allogeneic stem cell transplantation (allo SCT) in first CR from a suitable donor has been the standard strategy in adult Ph+ ALL patients, given their poor outcome with chemotherapy alone. Several recent reports have better defined the feasibility and outcome of this strategy in the pre-imatinib era. The introduction of imatinib and other TKIs has improved the likelihood of identifying a donor, as these agents provide durable responses in patients thereby allowing for the conduct of the appropriate donor searches.

Management of patients with relapse after prior chemotherapy or transplant has been even more challenging, with the main focus to induce a second CR and proceed with allo SCT.[14] Second-generation TKIs are becoming particularly useful in this setting, as they have produced second CRs even in this group of patients with generally dire prognosis.

Table 1
Selected chemotherapy trials in Ph + ALL

Study	Ph+, N (%)	CR %	Median EFS/CRD (Months)	Median OS (Months)
Bloomfield et al[100]	29 (17)	46	7	11
Gotz et al[101]	25	76	NA	8
Larsen et al[102]	30 (27)	70	7	11
GFCH[103]	127 (29)	59	5	NA
Secker-Walker et al[104]	40 (11)	83	13	11
Wetzler et al[105]	67 (29)	79	11	16
Faderl et al[106]	67 (13)	55, 90[a]	8, 10.8[a]	11.3, 16.5[a]
Dombret et al[31]	154	67	–	19% at 3 years[b]
Arico et al[9]	326	82	28% at 5 years[b]	40% at 5 years[b]
Schrappe et al[10]	61 (1)	75	38% at 5 years[b]	49% at 5 years[b]

Abbreviations: GFCH, Groupe Francais de Cytogenetique Hematologique; CR, complete remission; 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 at X years.

Imatinib and Imatinib-Containing Regimens

Imatinib in younger Ph+ acute lymphoblastic leukemia patients

With the introduction of effective TKIs, the treatment of Ph+ ALL patients is undergoing a revolutionary transformation, with improved outcomes not only for patients who are eligible for and are able to receive allo SCT but also for those who are not candidates for or are unable to undergo such treatment. In fact, for the first time, the role of transplantation in first CR has been questioned, with early follow-up of several studies demonstrating comparable outcomes for patients receiving imatinib-containing regimens with and without a transplant in first CR.[15–17]

Imatinib mesylate (Gleevec, Novartis Pharmaceuticals, Basel, Switzerland) binds the inactive moiety of the bcr-abl kinase, partially blocking its adenosine triphosphate (ATP) binding site, thereby preventing a conformational switch to the active tyrosine kinase (**Fig. 1**A). Significant clinical activity and favorable toxicity profile of imatinib in Ph+ ALL was evident in the initial phase 1 and 2 trials of the drug.[18–20] In the phase 2 study in patients with Ph+ ALL, imatinib induced CRs and complete marrow responses (marrow-CRs) in 29% of patients, which were sustained for at least 4 weeks in 6%.[19] However, the median estimated time to progression and OS were short, 2.2 and 4.9 months, respectively.[19] In a follow-up study, the extent of reduction in the *BCR-ABL* transcript levels in peripheral blood (PB) and bone marrow (BM), analyzed by quantitative polymerase chain reaction (Q-PCR), in the treated patients was predictive of response and median time to progression.[21] Other predictors of response such as pretreatment white blood cell count (WBC), presence of circulating blasts before treatment, duration of prior CR, and presence of a double Ph chromosome or up to two additional *BCR-ABL* fusion signals have also been reported.[22] The probability of achieving complete hematological response (CHR) and response duration was higher in patients with a baseline WBC less than 10×10^9/L, no circulating blasts pretreatment, a prior CR of at least 6 months, and no *BCR-ABL* amplification.[22] Of interest, presence of additional chromosomal aberrations or the size of the protein (p190 vs p210) did not affect the clinical outcome.

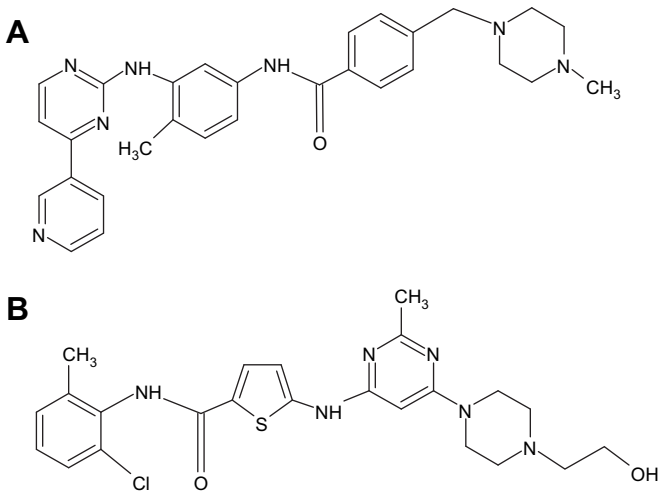

Fig. 1. (*A*) Imatinib. (*B*) Dasatinib.

Therefore, from these early studies it was clear that few, if any, patients can achieve durable responses with single-agent imatinib. At the same time, in vitro studies demonstrated synergistic or additive effects in Ph+ cell lines when imatinib was administered in combination with various chemotherapy agents, suggesting a potential role for these combinations in patients.[23–25] Several investigators explored the efficacy of imatinib in combination with chemotherapy for frontline treatment of Ph+ ALL patients, although initially the optimal schedule was debated, and concurrent as well as sequential schedules were investigated (**Table 2**).

In the first clinical trial reporting the combination of imatinib with chemotherapy, imatinib 400 mg was administered daily for the first 14 days of each of the eight cycles of the hyper-CVAD regimen (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose cytarabine and methotrexate).[15] This phase was followed by a maintenance phase whereby imatinib 600 mg was given continuously together with monthly vincristine and prednisone for 12 months.[15] A CR rate of 96% with a 2-year DFS of 85% was reported. Half of the initial cohort of 20 patients underwent allo SCT. These results were significantly superior to historical data using chemotherapy alone. Furthermore, molecular complete responses, as analyzed by Q-PCR, were reported in 60% of the patients. Of importance is that there was no unexpected toxicity related to the addition of imatinib to the regimen.

The same investigators have modified the regimen, with the final regimen including imatinib 600 mg on days 1 to 14 of induction, then 600 mg continuously with courses 2 to 8, followed by escalation to 800 mg as tolerated during 24 months of maintenance therapy with monthly vincristine and prednisone. Maintenance was interrupted by two intensification courses of hyper-CVAD and imatinib, and after its completion imatinib was administered indefinitely. Allo SCT was performed in first CR as feasible. In a follow-up report in 54 patients with untreated or minimally treated disease, a CR

Table 2
Clinical trials incorporating imatinib into frontline chemotherapy for Ph+ ALL

Study	N	Median Age (Range)	Imatinib and Chemo Schedule	CR %	Relapse %	EFS % (Years)	Survival % (Years)
Thomas et al[15,26]	45	51 (17–84)	Concurrent	93	22	68 (3)[a]	55 (3)
Yanada et al[16,28]	80	48 (15–63)	Concurrent	96	26	51 (2)	58 (20)
Lee et al[27]	20	37 (15–67)	Concurrent	95	32	62 (2)	59 (2)
Lee et al[42,43]	29	36 (18–55)	Alternating	79	4	78 (3)	78 (3)
Wassmann et al[29]	45	41 (19–63)	Concurrent	[a]	[a]	61 (2)	43 (2)
	47	46 (21–65)	Alternating	[a]	[a]	52 (2)	36 (2)
de Labarthe et al[30]	45	45 (16–59)	Concurrent	96	19	51 (1.5)	65 (1.5)
Delannoy et al[33]	30	66 (58–78)	Alternating	72	60	58 (1)	66 (1)
Vignetti et al[32]	30	69 (61–83)	+Prednisone	100	48	48 (1)	74 (1)
Ottmann et al[34]	28	68 (54–79)	Chemo→Concurrent	96	41	29 (1.5)	35 (1.5)
	27	–	Imatinib→Concurrent	50	54	57 (1.5)	41 (1.5)

Abbreviations: CR, complete remission; EFS, event-free survival.
[a] CR duration reported.

rate of 93% was reported for those with active disease.[26] Sixteen patients (33%) underwent allo SCT in first CR within a median of 5 months from start of therapy (range, 1–13). In the untreated group, 14 patients with a median age of 37 years underwent SCT in first CR whereas 33 patients with a median age of 53 years did not. The 3-year OS rates were similar (66% vs 49% with or without allo SCT, respectively, $P = .36$). The 3-year CR duration rate was 84% for patients who achieved molecular CR (2 of 16 had allo SCT) compared with 64% for those who did not (14 of 35 had allo SCT), $P = .1$; OS rates were similar regardless of molecular CR status. With a median follow-up of 52 months (range, 19–83+), 22% of the patients relapsed within a median of 15 months from the start of therapy (range, 8–42), including two after allo SCT without imatinib maintenance.[26]

Other investigators have reported the results of studies incorporating imatinib into ALL chemotherapy regimens (**Table 2**). In general, trials designed for younger patients have added imatinib for varying lengths and doses to standard regimens, whereas the emphasis in the older population has been to minimize poorly tolerated cytotoxic chemotherapy. The initial debates focusing on the optimal schedule, concurrent versus sequential imatinib, have been largely settled by several reports of good tolerability and improved efficacy of the concurrent treatment.

Lee and colleagues[27] reported on 20 patients with a median age of 37 years (range, 15–67 years) with newly diagnosed Ph+ ALL who received an induction regimen of daunorubicin, vincristine, prednisone, and L-asparaginase together with imatinib 600 mg daily on days 1 to 14. Imatinib 400 mg daily was also administered in the first 14 days of each course of consolidation. After the first 12 patients, imatinib was administered continuously in both induction and consolidation cycles. Nineteen (95%) patients achieved CR and 15 underwent allo SCT in first CR.[27] Median CR duration and median survival were significantly longer compared with a historical cohort of 18 patients treated with the same regimen but without imatinib.[27] The reported toxicities of the regimen included reversible hyperbilirubinemia in four patients.

The Japan Adult Leukemia Study Group (JALSG) reported on a concurrent induction regimen of imatinib, cyclophosphamide, daunorubicin, vincristine, and prednisolone.[16,28] Consolidation therapy consisted of odd courses of high-dose cytarabine and methotrexate, alternating with single-agent imatinib 600 mg daily for 28 days. Patients then received 2 years of maintenance with imatinib, vincristine, and prednisone. In the more recent report of 80 patients (median age 48 years, range, 15–63) a CR rate of 96% was reported.[16] A PCR-negative status was reported in 71% of patients at least at one point during their follow-up. Among the 57 patients who achieved PCR negativity, 17 patients had molecular relapse. Of them, seven patients had hematological relapse, six underwent allo SCT, and four were in continuous CR without allo SCT. Allo SCT was conducted in 49 patients including 39 who underwent allo SCT in first CR. The 1-year event-free survival (EFS) and OS were estimated to be 60% and 76%, respectively, which were significantly better than historical controls treated without imatinib ($P<.0001$ for both). The probability of survival at 1 year was 73% and 85% for those who received or did not receive allo SCT, respectively.

To establish the best strategy of incorporating imatinib into ALL chemotherapy, The German Multicenter Acute Lymphoblastic Leukemia (GMALL) trial evaluated 92 patients (median age 46 years, range 21–65 years) in two schedules.[29] Imatinib was administered alternating with chemotherapy cycles in the first cohort of patients; then it was administered concurrently with chemotherapy throughout the second induction phase, consolidation, and up to allo SCT in the second cohort. Before consolidation, PCR negativity rates of 52% and 19% were reported in the concurrent and alternating cohorts, respectively. A poor hematological response to the first

induction cycle of chemotherapy was compensated by subsequent concurrent administration of imatinib with chemotherapy.[29] In each cohort, 77% of patients underwent allo SCT, and toxicity was acceptable for both schedules. The investigators concluded that the concurrent regimen had a greater antileukemic efficacy. However, this greater activity did not translate to improvements in EFS and OS.[29]

In the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAAPH) 2003 study, imatinib was started with cytarabine and mitoxantrone (HAM) consolidation in good early responders (corticosteroid and chemosensitive ALL), or earlier during the induction course in combination with dexamethasone and vincristine in poor early responders (corticosteroid or chemoresistant ALL). Imatinib was then continuously administered until allo SCT.[30] Overall CR and Q-PCR negativity rates were 96% and 29%, respectively. The CR rate was significantly higher compared with the previous report from the pre-imatinib era by the same group (96% vs 71%, $P<.001$), and the DFS and OS were significantly longer ($P = .02$ and 0.05, respectively).[30,31] Furthermore, patients younger than 55 years were eligible for allo SCT and all 22 with a donor underwent SCT. Early results of a study by the Children's Oncology Group in which imatinib at 340 mg/m^2 was administered for an increasing number of days in combination with an intensive chemotherapy backbone seem to confirm the benefit of the addition of imatinib, even in the pediatric population, and irrespective of the availability of a donor.[17]

Therefore, it is clear that the addition of imatinib to the initial therapy for patients with Ph+ ALL has significantly improved their outcome. Despite relatively short follow-up and variations in the design and schedule of treatment, higher response rates, improved feasibility of allo SCT. and improved EFS and OS rates were observed in all trials.

Imatinib in elderly Ph+ acute lymphoblastic leukemia patients

The question of the more imatinib and less chemotherapy approach has been of particular interest in the elderly population, who are less tolerant of the intensive chemotherapy regimens used in ALL, are less likely to be candidates for allo SCT, and comprise a significant portion of patients with this disease.[12] Several trials have examined various approaches in this population (**Table 2**).

In the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) study, 30 patients with Ph+ ALL, 60 years and older, were treated with imatinib 800 mg as well as prednisone 40 mg/m^2 daily from days 1 to 45.[32] Twenty-nine were assessable for response and all (100%) achieved CR. Molecular CR was achieved only in 1 of the 27 evaluable patients.[32] The median CR duration and survival were 8 months and 20 months, respectively.[32] Fourteen patients relapsed after a median of 4 months (range, 3–28 months). Two patients died in CR and 13 were alive in continuous remission after a median of 10 months (range, 1–32 months).[32] In a study by Group for Research on Adult Acute Lymphocytic Leukemia (GRAALL), patients 55 years or older were treated with chemotherapy-based induction after a pre-phase of steroids.[33] This phase was followed by a consolidation phase of steroids and imatinib, and 10 maintenance blocks of alternating chemotherapy, including two imatinib-containing blocks. Among the 30 patients treated, a CR rate of 72% was reported, with additional patients achieving CR after salvage imatinib.[33] The outcome was significantly better than in historical patients treated by the same group, with 1-year OS of 66% versus 43% ($P = .005$), and 1-year relapse-free survival of 58% versus 11% ($P = .0003$).

Ottmann and colleagues[34] conducted a randomized trial of imatinib monotherapy versus standard induction therapy in 55 patients with a median age of 67 years (range, 54–79 years). The CR rate was 96% in the imatinib-treated arm versus 50% in the

patients receiving induction chemotherapy ($P = .0001$). Severe adverse events were significantly more frequent during induction with chemotherapy. Patients in either treatment arm then received imatinib 600 mg daily in combination with all successive cycles of chemotherapy, which were administered irrespective of response to induction. The estimated OS for all patients was 42% at 2 years, with no significant difference between the 2 arms.[34] The molecular CR rates did not differ with either approach but PCR negativity occurred earlier in the imatinib induction arm. Median DFS was significantly longer in the patients achieving PCR-negative status (18.3 months vs 7.2 months, $P = .002$).

Role of Allogeneic Stem Cell Transplantation Before and After Imatinib Era

Pre-imatinib era

With the incorporation of imatinib and other TKIs in the treatment of Ph+ ALL, the role of allo SCT is undergoing transformation. In the past, it was the only strategy that had a significant curative potential. However, it was limited in its application by the availability of suitable donors, and by its diminished feasibility and effectiveness in older patients, those with comorbid conditions, and those with active leukemia at the time of transplantation. The outcome after allo SCT in the pre-imatinib era has been better characterized by several recent reports. Laport and colleagues[35] reported the outcomes for the largest series to date of uniformly treated Ph+ ALL patients. From 1985 to 2005, 79 patients with Ph+ ALL, with a median age of 36 years, received a matched sibling transplant following total body irradiation (TBI) and etoposide-based conditioning, and cyclosporine-based graft versus host disease (GVHD) prophylaxis. For patients transplanted in first CR, the 10-year OS and cumulative incidence of nonrelapse mortality (NRM) were 54% and 31%, respectively. Acute GVHD, grades 2 to 4, was noted in 35% of patients, with 13% of patients developing chronic extensive GVHD. Of note, patients transplanted with PB stem cells were twice as likely to develop chronic GVHD compared with patients who received BM stem cells, confirming results of other randomized studies assessing the impact of stem cell source on transplant outcome.[36,37] The median time to relapse was 12 months (range, 1–27 months), and all deaths due to NRM occurred within 3 years of allo SCT.[35]

The results of single-center studies have been corroborated in large, multicenter studies designed to prospectively assess the role of allo SCT in adult ALL patients. In the largest trial to date, 267 Ph+ ALL patients were treated between 1993 and 2004 as part of the MRC UKALL XII/ECOG E2993 study.[38] Patients with Ph+ disease who were younger than 55 years and had achieved CR were assigned to a matched sibling or matched unrelated donor (MUD). Patients without a donor or with a performance status that prohibited allo SCT were eligible for randomization to continued chemotherapy versus autologous SCT; very few patients were actually randomized, with the majority of patients receiving continued chemotherapy.[38] The conditioning regimen for the allo SCT consisted of TBI and etoposide, and a cyclosporine-based GVHD prophylaxis regimen was recommended; imatinib was not used in the patients reported in this series. Twenty-eight percent of patients received a matched-related or unrelated donor allo SCT in first CR. At 5 years, OS was 44% following sibling SCT, 36% following MUD SCT, and 19% following chemotherapy, with treatment-related mortality (TRM) of 27% following sibling SCT and 39% following MUD SCT.[38] After adjusting for differences in age and WBC at presentation in the two groups and after excluding chemotherapy-treated patients who relapsed or died before the median time to allo SCT, only relapse-free survival remained significantly better in the allo SCT group; the TRM rate became significantly lower for the chemotherapy group, and OS became nonsignificantly worse in the allo SCT group, underscoring the

need to carefully weigh the benefit of disease control with the TRM associated with allo SCT. An intention-to-treat analysis, using the availability of a matched sibling donor, showed no significant difference in survival between the two groups (34% with and 25% without a donor).[38]

The results of this trial are consistent with the conclusions of two earlier studies, the LALA-87 and LALA-94 trials, which were designed to prospectively evaluate the role of allo SCT in first CR.[31,39] Analyzed on an intention-to-treat basis, the LALA-87 trial showed a statistically significant advantage for allo SCT versus chemotherapy for patients with high-risk ALL, including Ph+ patients, with 10-year survival rates of 44% and 11%, respectively.[39] In the follow-up LALA-94 trial, the advantage of allo SCT over chemotherapy in Ph+ ALL patients was confirmed (estimated survival at 3 years 37% vs 12%, $P = .02$).[31] Furthermore, the advantage of a molecular response before SCT was demonstrated, with 3-year survival estimated at 54% for the group achieving a negative PCR versus 19% for those remaining *BCR-ABL* positive.[31] This result is in agreement with studies in the pediatric population in which the level of residual disease before allo SCT correlates with outcome after SCT.[40,41]

Post-imatinib era

The incorporation of imatinib into standard ALL therapy has improved the ability to undergo allo SCT in first CR, resulting in improved OS rates of 43% to 78% at 1 to 3 years of follow-up.[15,16,29,30] As discussed previously, even before imatinib, patients in molecular remission at time of allo SCT had a longer DFS.[31] As a result, interim monotherapy with imatinib has been used to reduce the disease burden prior to allo SCT.[42,43] In a study by Lee and colleagues,[42,43] interim cycles of imatinib between induction and consolidation, and between consolidation and allo SCT significantly improved the DFS and OS compared with a historical group of patients treated with the same chemotherapy regimen but without imatinib. The patients' *BCR-ABL*/*ABL* ratios declined by a median of 0.77 and 0.34 logs after each of the two cycles of imatinib.[42,43] As a result, a significantly higher proportion of patients proceeded to allo SCT in first CR. Therefore, such interim imatinib therapy not only improves the likelihood of allo SCT to be conducted in Ph+ ALL patients but also allows it to occur in a more favorable status.[44] Of note, thus far the early results of studies incorporating imatinib into pretransplant therapy have not demonstrated a clear survival difference between patients who receive an allo SCT for consolidation compared with those who do not.[15,16,29,30] Thus, whether consolidation with allo SCT in first CR will remain the standard of care for Ph+ ALL will depend on the durability of the remissions achieved with chemotherapy plus imatinib regimens.

Radich and colleagues[45] had shown that Ph+ ALL patients who remained PCR-positive after allo SCT had a significantly higher incidence of relapse than PCR-negative patients. Therefore, use of imatinib in the posttransplant setting to eradicate minimal residual disease (MRD) has been investigated by several groups.[46–48] In the study by Wassmann and colleagues,[47] 27 Ph+ ALL patients received imatinib 400 mg daily on detection of MRD after SCT. The dose could be escalated to 600 mg and 800 mg in patients remaining PCR-positive. *BCR-ABL* transcripts were undetectable in 14 (52%) of the patients, after a median of 1.5 months of imatinib therapy (range, 0.9–3.7 months). Failure to achieve a molecular remission within 6 weeks of starting imatinib predicted relapse, occurring in 12 of 13 (92%) patients at a median of 3 months. DFS in patients with molecular CR at 12 and 24 months was 91% and 54% compared with only 8% in patients remaining MRD-positive after 12 months.[47] These data suggested the benefit of prophylactic administration of imatinib in the post allo SCT setting.[48] Imatinib could be administered safely from

the time of engraftment at a dose intensity comparable to that used in primary therapy. Similar strategies combining interferon and imatinib to maintain remission have also been investigated.[49,50]

As evident in the MRC UKALL XII/ECOG 2993 study, TRM overcomes any survival advantage for transplant in older patients. Because the incidence of ALL, particularly the Ph+ subtype, increases in adults older than 50 years, transplant approaches with reduced TRM such as nonmyeloablative regimens are needed. Martino and colleagues[51] reported the largest series of nonmyeloablative SCT in ALL. These investigators reported a TRM of 23%, OS of 31%, and disease progression of 49% at 2 years among 27 patients with a median age of 55 years. A higher relapse rate was observed for patients transplanted with overt disease compared with those transplanted in CR (60% vs 33%, respectively). These data suggest that this strategy is feasible in older patients in CR, but must be validated in multicenter, prospective studies.

Beyond first remission, allo SCT is curative in only a small fraction of ALL patients, with long-term OS ranging between 5% and 43%, the primary cause of failure being relapse (>50%).[38,52–55] In a study of 60 adult patients with advanced ALL (primary refractory n = 8, first relapse n = 52), including 14 patients with Ph+ disease, those who did not undergo reinduction chemotherapy after relapse had a better outcome, with 5-year OS 47% versus 18%.[55] The investigators suggested that patients who did not undergo salvage chemotherapy before SCT sustained less TRM, leading ultimately to a better outcome.[55] In the subset of patients who relapsed in the MRC ECOG/UKALL study, patients who were able to receive a matched sibling transplant had the best survival at 5 years (23%).[56] Factors predicting a better outcome were young age (OS 12% for patients <20 years old versus 3% for patients >50 years old) and long duration of first remission (OS 11% for CR1 >2 years versus 5% for CR1 <2 years).[56]

With current induction regimens, only 5% to 10% of newly diagnosed Ph+ ALL adults fail to achieve remission with initial induction chemotherapy, and additional attempts at induction chemotherapy may be unsuccessful. Several studies suggest that patients with a human leukocyte antigen (HLA)-identical sibling can benefit if they proceed directly to allo SCT without undergoing a second attempt at induction therapy.[57,58] In the largest study, 38 patients with ALL failing to achieve remission received HLA-identical sibling transplants without reinduction.[57] Approximately 35% of these patients with refractory disease achieved long-term DFS. A second study with 22 patients (5 with ALL) with refractory disease had a similar survival of 38% following HLA-matched sibling transplants.[58] Other studies suggest lower survival rates of 20% or less for these refractory patients.[57,59] Nevertheless, allogeneic transplant should be considered for patients with relapsed/refractory disease who otherwise have a dismal chance of long-term survival.

In conclusion, transplant offered superior disease control compared with chemotherapy in the pre-TKI era, and allo SCT with a matched sibling or unrelated donor was recommended for all patients in first CR. The addition of TKIs to standard ALL therapy seems to improve disease control, albeit with relatively short follow-up. Allo SCT in first CR remains standard, but older or frail patients may be monitored closely with Q-PCR and transplanted at time of increasing *BCR-ABL* transcript levels. Alternatively, nonmyeloablative transplants with an expected lower TRM may be considered. Allo SCT with matched sibling or unrelated donors should be recommended for all patients with primary refractory or relapsed disease. Furthermore, alternative donor transplants should be considered in these patients, despite their significant TRM and relapse rates of up to 40%. Small patient numbers and heterogeneity in

remission status limit conclusions regarding the use of umbilical cord blood transplants. An estimated 20% to 50% of patients transplanted in remission can achieve long-term disease control; relapse and engraftment remain significant issues.[60]

Resistance to Imatinib

Both acquired and intrinsic resistance to imatinib has been described in Ph+ ALL patients. Acquired imatinib resistance may be due to *BCR-ABL*–dependent mechanisms such as bcr-abl overexpression or mutations in the kinase domains (KD) (**Table 3**).[61,62] Resistance may also arise through *BCR-ABL*–independent mechanisms such as pharmacokinetic factors reducing the availability of imatinib within Ph+ cells, or through activation of alternative signaling pathways such as the Src-kinase related pathways.[63–67]

Although several KD mutations have limited consequence, those that interfere with imatinib binding to the bcr-abl protein have been identified as a major mechanism of acquired resistance in patients with CML.[61,62,68] These include (1) mutations that directly impede contact between imatinib and bcr-abl, such as T315I and F317L, and (2) mutations in the ATP-binding P-loop or in the activation loop, which alter the spatial conformation of the protein.[61,62,69,70] Data on the frequency and spectrum of these mutations in Ph+ ALL is more limited. Two early studies in patients with advanced Ph+ lymphoid leukemias identified 5 different KD mutations in 14 of 17 patients with acquired imatinib resistance.[71,72] In one report E255K/V mutations were noted in 67% of patients, but this was not confirmed by the other study.[71,72] However, in these studies KD mutations occurring before initiation of therapy with imatinib that could potentially account for primary resistance were not identified. More recently the same investigators, using a more sensitive cloning and sequencing strategy, were able to demonstrate the presence of low-level KD mutations in imatinib-naïve patients.[73] In a follow-up study in a larger cohort of elderly patients enrolled into the GMALL randomized study,[34] approximately 40% of patients with imatinib-naïve with no or minimal prior exposure to chemotherapy harbored a small leukemic clone (allele frequency of 2%, range 0.1%–2%) with these mutations.[74] The frequency of the mutant allele at the time of diagnosis was always below the level of detection by direct cDNA sequencing, and ATP-binding P-loop mutations were the dominant type, accounting for 83% of the mutations with the other 17% being T315I. It is remarkable

Table 3
Reported potential mechanisms of resistance to imatinib

Mechanisms related to cellular uptake and retention of imatinib
Increased MDR1 expression[107]
Reduced hOCT1 mediated influx[67,108]
Increased binding to α1-acid glycoprotein-1[109]
BCR-ABL dependent mechanisms
BCR-ABL overexpression[61]
BCR-ABL kinase domain mutations[61,62]
BCR-ABL independent mechanisms
Activation of alternate signaling pathways such as Src[65]
Clonal evolution[110]
Miscellaneous
Noncompliance
Stem cell quiescence[111]

that preexistence of mutations including T315I did not adversely affect the CR rate or the achievement of molecular CR when compared with patients who only had unmutated *BCR-ABL* at diagnosis.[74] This finding raises the hypothesis that these clones were eradicated by chemotherapy.

Only the presence of T315I at diagnoses was associated with a more rapid relapse; however, nearly all of the patients with a detectable mutation at diagnosis relapsed as opposed to only 50% of patients with unmutated BCR-ABL. Among the patients who relapsed, 84% harbored mutations, with the most frequent site of mutations being P-loop (58%) and T315I (19%). Comparing the mutations at diagnosis and relapse, only 1 of 11 patients with detectable mutation at diagnosis had a switch. On the other hand, 67% of patients with no mutation at baseline were found to have a dominant mutant clone at relapse.[74] Jones and colleagues[75] have also recently reported the presence of KD mutations in most patients with relapsed disease following imatinib therapy. KD mutations were detected in 88% of patients who had received either imatinib (n = 11) or dasatinib (n = 1), and in 86% of patients who had had two or more prior TKIs compared with none of the patients who never received TKIs.[75] A limited spectrum of mutations, mostly Y253H, T315I, and F317L, were noted, which were not present before treatment with TKIs in those with available samples. Other investigators have also reported a high frequency of mutations at relapse, suggesting a pivotal role for the *BCR-ABL* KD mutations in acquired imatinib resistance in Ph+ ALL patients.[75,76] Whether such acquired imatinib resistance is a result of outgrowth of small clones with mutant KD existing before the initiation of imatinib, or the effect of selection leading to the emergence of mutations after the initiation of and continuous exposure to TKIs, requires further studies.[74,75]

A new mechanism of resistance involves the expression of spliced isoforms of Ikaros (*IKZF1*).[77] Ikzf1 functions as a critical regulator of normal lymphocyte development and is involved in the rapid development of leukemia in mice expressing non-DNA binding isoforms.[78] The Ik6 isoform, lacking all 4 N-terminal zinc fingers responsible for DNA binding, was detected in 43 of 47 (91%) Ph+ ALL patients resistant to imatinib or dasatinib.[77] In addition, the expression level of Ik6 correlated with the *BCR-ABL* transcript level. Restoring Ikzf1 function would be of great benefit in this condition.

Finally, stromal support was proposed as an additional mechanism of resistance to TKIs.[79] Cells with low expression of *BCR-ABL* were able to grow in the presence of stroma. The stromal effect did not require cell-cell contact and the stromal-cell derived factor 1α, the ligand to the chemokine receptor 4 (CXCR4), could substitute for the presence of the stromal cells. Interfering with the stroma-lymphoblast interaction, possibly by the CXCR4 inhibitor plerixafor (AMD3100), could be of benefit in eradicating Ph+ ALL cells.

Second-Generation Tyrosine Kinase Inhibitors

The development of resistance and intolerance to imatinib in Ph+ leukemia patients has fuelled the search for alternative, second-generation inhibitors capable of overcoming the resistance.[80–82] Dasatinib is a dual Src and Abl kinase inhibitor that binds both active and inactive moieties of the bcr-abl protein, and is approximately 325 times more potent against the kinase in preclinical studies (**Fig. 1**B).[80] The inhibition of other kinases, particularly Src, may be important in overcoming imatinib resistance, particularly in patients with lymphoid leukemias in whom Src-kinase activity may be important in the pathogenesis of the disease.[83] Dasatinib is active in vitro against all imatinib-resistant BCR-ABL mutants with the notable exception of T315I.[80] It has demonstrated significant activity in phase I and II studies in Ph+ leukemia patients

who were resistant to or intolerant of imatinib. Cortes and colleagues[84] reported the results of a phase II trial in which patients with blast phase of CML who had failed imatinib were treated with dasatinib 70 mg orally twice daily. Among 42 patients with lymphoid blast phase, 31% achieved a major hematological response (HR) and 50% a major cytogenetic response, mostly CRs. Response rates were similar in patients with or without imatinib-resistant *BCR-ABL* mutations. Ottmann and colleagues[85] conducted a phase 2 study of dasatinib in 36 Ph+ ALL patients after failing imatinib. The median age of the patients was 46 years (range, 15–85 years). Major HR was achieved in 15 (42%) of patients and cytogenetic CR in 21 (58%). Six patients had a baseline T315I mutation and none responded, but response rates were similar in patients with other mutations compared with those with no mutations.[85] More recent data have suggested that administering dasatinib once daily in CML or Ph+ ALL patients produces similar responses and is associated with a better toxicity profile, including a lower incidence of grade III and IV myelosuppression or pleural effusions.[86] In another report it was suggested that this regimen was effective in achieving CR in patients who had relapsed from prior, mostly imatinib-based therapy.[87]

Based on the significant activity of dasatinib against *BCR-ABL*, and impressive data in patients with relapsed disease, the authors have conducted a phase 2 study of combining the hyper-CVAD regimen with dasatinib, administered at 50 mg orally twice daily for the first 14 days of each of the eight induction/consolidation chemotherapy cycles, as frontline therapy.[88] Patients would then receive dasatinib continuously and indefinitely, with monthly cycles of prednisone and vincristine for the first 2 years. A lower dasatinib dose was chosen to avoid excessive myelosuppression when combined with intensive chemotherapy. Preliminary data have been recently reported demonstrating the feasibility of this regimen in relapsed and previously untreated patients.[88] Among 28 patients with newly diagnosed disease (median age 52 years, range 21–79 years), 26 (93%) achieved CR after one course of treatment; 20 of 26 (81%) achieved a cytogenetic CR after 1 cycle, and 19 (68%) achieved a major molecular response including 14 (50%) with molecular CR. With a median follow-up of 10 months (range, 2–21 months), 21 were alive and 18 alive in CR, 2 died at induction and 3 died in CR; 5 patients had relapsed with a median CR duration of 47 weeks in the relapsing patients; 2 relapsing patients died.[88] Of note, *BCR-ABL* mutations were identified in 4 of the 5 relapsing patients (including 3 with T315I and 1 with F359V).[88]

Early reports of ongoing studies have suggested improved outcomes in older patients using dasatinib-based regimens for newly diagnosed patients. In a study by the European Working Group on adult ALL (EWALL), patients older than 55 years received an induction schedule of vincristine and dexamethasone repeated weekly for 4 weeks, followed by consolidation methotrexate and asparaginase alternating with cytarabine for a total of 6 cycles.[89] Dasatinib was administered at 140 mg daily during the induction and at 100 mg/day sequentially during the consolidation and maintenance courses. A CR rate of 95% was reported in the first 22 patients treated. Only 1 relapse and 3 deaths in CR were reported at a median follow-up of 3.6 months.[89] In the GIMEMA LAL 1205 study, dasatinib 70 mg twice daily was administered for 12 weeks, in combination with prednisone and intrathecal chemotherapy, to treat adult patients with newly diagnosed Ph+ ALL.[90] Among the first 48 patients (median age, 54 years; range, 24–76 years) 34 were evaluable for response, and a CR rate of 100% was reported with no deaths attributable to treatment.[90] With a median follow-up of 11 months, survival at 10 months was 81%. Nine patients

had relapsed, with five showing a T315I, one an E255K, and two without mutations. Details of consolidation treatment were not provided.[90]

Existence of *BCR-ABL* mutations that may induce resistance to dasatinib is of significant concern.[91] Mutations in the gatekeeper region of *BCR-ABL*, in particular T315I, confer resistance to dasatinib (as well as imatinib and other available TKIs). Crystal studies have demonstrated that the aromatic ring in the side chain of phenylalanine 317 directly interacts with the pyrimidine and thiazole rings of dasatinib.[92] Furthermore, in the in vitro saturation mutagenesis, several amino acid substitutions affecting residue 317 have been reported to induce dasatinib resistance, including both the imatinib-resistant F317L and other variants like F317V, F317I, and F317S. In cellular assays, the F317L has been shown to induce an approximately 10-fold increase of dasatinib IC_{50} with respect to wild-type *BCR-ABL*.[93] As with imatinib-based therapy, at present it is not clear whether these mutants exist pretherapy and dasatinib treatment induces their overgrowth, or if their development is a direct result of treatment with the TKIs. Other second-generation TKIs, including nilotinib and bosutinib as well other investigational agents have been evaluated in phase 1 and 2 trials. Of potential interest are agents with activity against the T315I mutants.

Central Nervous System Disease

Central nervous system (CNS) involvement is common in ALL, with up to 6% of patients having evidence of involvement at diagnosis and without adequate prophylaxis, Up to 30% of patients will develop CNS disease during treatment and follow-up.[94,95] However, with routine CNS-directed treatment, this risk has subsided to less than 10%. Several recent studies have reported a relatively high incidence of isolated CNS relapse in Ph+ acute leukemia patients, with generally unfavorable outcomes.[96,97] In the study by Leis and colleagues,[97] 5 of 24 (21%) Ph+ acute leukemia (ALL or CML lymphoid blast phase) patients who were treated with imatinib and without intensive chemotherapy or specific CNS prophylaxis developed CNS disease despite achieving a CR. Simultaneous plasma and cerebrospinal fluid (CSF) imatinib levels were measured in four subsequent patients, and imatinib levels were noted to be two logs lower in the CSF than in plasma, with the CSF levels being below the level required for bcr-abl inhibition. Another report confirmed an almost 100-fold lower imatinib level in the CSF compared with plasma in a patient with relapsed Ph+ ALL and concurrent CNS disease.[98] These studies suggest that imatinib poorly penetrates the blood-brain barrier, and underscore the need for adequate CNS-directed therapy in patients receiving imatinib-based therapy. At least in part, this may be because imatinib is a substrate for the drug efflux P-glycoprotein with the latter's high expression in the CNS.

Imatinib and dasatinib have been compared in a preclinical mouse model of intracranial Ph+ leukemia for their ability to penetrate the blood-brain barrier.[99] Dasatinib has antileukemic activity in the multidrug-resistant K562/ADM, with a high expression of P-glycoprotein, and as such may have a better penetrance of the blood-brain barrier.[99] In the mouse model, dasatinib led to the regression of CNS disease and improved survival, whereas imatinib was unable to inhibit the intracranial tumor growth. Furthermore, clinical responses to dasatinib in patients with imatinib-resistant disease involving the CNS have been reported, with responses being durable in some patients.[99] Furthermore, KD mutational analysis on the blasts from the CSF of two patients who experienced a CNS relapse while receiving dasatinib demonstrated the presence of dasatinib-resistant mutations, suggesting a selection pressure further indicating its CNS penetration.[99] Prospective studies evaluating the dasatinib CSF

Table 4
Selected new agents being evaluated in Ph+ leukemias

Drug	Mechanism of Action
Bosutinib	Bcr-Abl and Src-kinase inhibitor
Homoharringtonine	Inhibition of protein synthesis, induction of differentiation and apoptosis
PHA739358	Bcr-Abl and Aurora kinase A, B, and C inhibitor
AP24534	Bcr-Abl, FLT3, and FGF1-R inhibitor
DCC2036	Bcr-Abl inhibitor (binds the "switch pocket")
XL228	Bcr-Abl, Src and IGF1-R inhibitor

levels and its ability to decrease the incidence of CNS relapse are necessary to confirm these data.

Future Challenges in Ph+ Acute Lymphoblastic Leukemia

The introduction of effective TKIs in the treatment of Ph+ ALL has introduced several avenues of research in a disease that was hitherto difficult to treat. In the younger patients, the standard therapy should include combination of chemotherapy with one of the TKIs, likely imatinib but potentially dasatinib, with further maturation of emerging data. In the older patients who are less able to tolerate intensive chemotherapy regimens, rationally designed combinations including dasatinib, in addition to the careful monitoring for response, MRD, and toxicity to decide on the continuation of treatment may further improve the outcome. The emergence or resurgence of KD mutations, particularly those resistant to the available TKIs (such as T315I), is a significant concern that requires careful design of potential strategies to circumvent it. Several new TKIs are in development, with potential efficacy against clones resistant to first- and second-generation TKIs, including T315I mutants (**Table 4**). The role of allo SCT will likely continue to be refined, incorporating TKI-based strategies before and after allo SCT to maximize the benefits from all of the therapeutic armamentarium against this disease.

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