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## PHILADELPHIA CHROMOSOME POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

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### INTRODUCTION AND 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 *Abl* gene on chromosome 9.<sup>1,2</sup> The protein product of the fusion gene, BCR-ABL, has enhanced tyrosine kinase activity leading to the constitutive activation of a number of downstream pro-proliferative and pro-survival signaling pathways, and hence to leukemogenesis.<sup>3</sup> 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.<sup>4</sup> The incidence rises with age and it occurs in approximately 50% of patients older than 50 years.<sup>5</sup>

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<sup>bcr-abl</sup> protein is found in over two thirds of patients with Ph+ ALL and the larger p210<sup>bcr-abl</sup> protein, typical of chronic myeloid leukemia (CML) but is also encountered in about a third of Ph+ ALL patients.<sup>6</sup> In experimental models, the p190<sup>bcr-abl</sup> protein has a higher tyrosine kinase activity and is more efficient in stimulating the growth of lymphoid cells.<sup>6,7</sup> However, using

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traditional chemotherapy regimens, clinical outcomes in patients carrying either of the two proteins have been generally similar.<sup>6,8</sup>

## TREATMENT OF ADULTS AND CHILDREN WITH PH+ ALL

### Historical perspectives

Prior to the introduction of imatinib, the outcome of patients with Ph+ ALL was poor. Although complete remission (CR) could be achieved in a the majority the of patients (60%–90%), the median CR duration was considerably shorter than that seen in patients with Ph- disease, leading to very few long term survivors. (Table 1) This 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.<sup>9,10</sup> On the other end of the age spectrum, specifically those older than 50–60 years of age, the outcome was particularly dismal with high treatment-related mortality, low CR rates and short disease-free survival (DFS) and overall survival (OS).<sup>5,11,12</sup>

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.<sup>13</sup> This may be indicative of 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 tyrosine kinase inhibitors 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.<sup>14</sup> 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.

### Imatinib and imatinib containing regimens

**Imatinib in younger Ph+ ALL patients**—With the introduction of effective tyrosine kinase inhibitors, 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 a number of studies demonstrating comparable outcomes for patients receiving imatinib containing regimens with and without a transplant in first CR.<sup>15–17</sup>

Imatinib mesylate (Gleevec<sup>®</sup>, Novartis Pharmaceuticals, Basel, Switzerland) binds the inactive moiety of the bcr-abl kinase, partially blocking its ATP binding site, thereby preventing a conformational switch to the active tyrosine kinase (Figure 1a). Significant clinical activity and favorable toxicity profile of imatinib in Ph+ ALL was evident in the initial phase I and II trials of the drug.<sup>18–20</sup> In the phase II 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%.<sup>19</sup> However, the median estimated time to progression and overall survival were short, 2.2 and 4.9 months, respectively.<sup>19</sup> 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 (QPCR) in the treated patients was predictive of response and median time to progression.<sup>21</sup> Other predictors of response such as pre-treatment white blood count (WBC), presence of circulating blasts prior to treatment, duration of prior CR, presence of a double Ph chromosome or up to 2 additional *BCR-ABL* fusion signals have also been reported.<sup>22</sup> The probability of achieving complete hematological response (CHR) and response duration was higher in patients with a baseline WBC < 10 × 10<sup>9</sup>/L, no circulating blasts pretreatment, a prior CR of at least 6 months, and no *BCR-ABL* amplification.<sup>22</sup> Of interest, presence of additional chromosomal aberrations, or the size of the protein (p190 versus p210) did not affect the clinical outcome.

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.<sup>23–25</sup> 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 8 cycles of the hyperCVAD regimen (fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone, alternating with high dose cytarabine and methotrexate).<sup>15</sup> This was followed by a maintenance phase where imatinib 600 mg was given continuously together with monthly vincristine and prednisone for 12 months.<sup>15</sup> 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 were significantly superior results compared with historical data using chemotherapy alone. Furthermore, molecular complete responses, as analyzed by Q-PCR, were reported in 60% of the patients. Importantly, 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 1–14 of induction, then 600 mg continuously with courses 2–8, followed by escalation to 800 mg as tolerated during 24 months of maintenance therapy with monthly vincristine and prednisone. Maintenance was interrupted by 2 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 rate of 93% was reported for those with active disease.<sup>26</sup> Sixteen pts (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 median age of 37 yrs 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% versus 49% with or without allo SCT, respectively,  $p=0.36$ ). The 3-yr CR duration rate was 84% for patients who achieved molecular CR (2 of 16 had allo SCT) compared to 64% for those who did not (14 of 35 had allo SCT),  $p=0.1$ ; 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.<sup>26</sup>

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 et al 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 1–14.<sup>27</sup> 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.<sup>27</sup> Median CR duration and median survival were significantly longer compared to a historical cohort of 18 patients treated with the same regimen but without imatinib.<sup>27</sup> The reported toxicities of the regimen included reversible hyperbilirubinemia in 4 patients.

The Japan Adult Leukemia Study Group (JALSG) reported on a concurrent induction regimen of imatinib, cyclophosphamide, daunorubicin, vincristine and prednisolone.<sup>16,28</sup> 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.<sup>16</sup> 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 patients 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 ( $p < 0.0001$  for both). The probability of survival at 1 year was 73% and 85% for those who received or did not receive allo SCT, respectively.

In order 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.<sup>29</sup> 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. Prior to 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.<sup>29</sup> In each cohort, 77% of patients underwent allo SCT and toxicity was acceptable for both schedules. The authors concluded that the concurrent regimen had a greater anti-leukemia efficacy. However, this greater activity did not translate to improvements in EFS and OS.<sup>29</sup>

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 and/or chemoresistant ALL). Imatinib was then continuously administered until allo SCT.<sup>30</sup> Overall CR and QPCR negativity rates were 96% and 29%, respectively. The CR rate was significantly higher compared to the previous report from the pre-imatinib era by the same group (96% versus 71%,  $p < 0.001$ ) and the DFS and OS were significantly longer ( $p = 0.02$ , and  $0.05$ , respectively).<sup>30,31</sup> 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 where imatinib at  $340 \text{ mg/m}^2$  was administered for an increasing number of days in combination with an intensive chemotherapy backbone seems to confirm the benefit of the addition of imatinib even in the pediatric population and irrespective of the availability of a donor.<sup>17</sup>

Therefore, it is clear that the addition of imatinib to the initial therapy of 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+ ALL patients**—The question of 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.<sup>12</sup> 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  $800 \text{ mg}$  as well as prednisone  $40 \text{ mg/m}^2$  daily from days 1 to 45.<sup>32</sup> Twenty-nine were assessable for response and all (100%) achieved CR. Molecular CR was achieved only in 1 of the 27 evaluable patients.<sup>32</sup> The median CR duration and survival were 8 months and 20 months, respectively.<sup>32</sup> 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).<sup>32</sup> 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.<sup>33</sup> This was followed by consolidation phase of steroids and imatinib and 10 maintenance blocks of alternating chemotherapy, including 2 imatinib containing blocks. Among the 30 patients treated, a CR rate of 72% was reported with additional patients achieving CR after salvage imatinib.<sup>33</sup> The outcome was significantly better than in historical patients treated by the same group with the 1-year OS of 66% versus 43% ( $p=0.005$ ), and 1-year relapse-free survival of 58% versus 11% ( $p=0.0003$ ).

Ottmann et al 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).<sup>34</sup> The CR rate was 96% in the imatinib treated arm versus 50% in the patients receiving induction chemotherapy ( $p=0.0001$ ). 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.<sup>34</sup> The molecular CR rates did not differ with either approach but PCR negativity occurred earlier in the imatinib induction arm. Median DFS survival was significantly longer in the patients achieving PCR negative status (18.3 months versus 7.2 months,  $p=0.002$ )

### 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 which 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 co-morbid 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 et al reported the outcomes for the largest series to date of uniformly treated Ph+ ALL patients.<sup>35</sup> From 1985–2005, seventy-nine 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 overall survival (OS) and cumulative incidence of non-relapse mortality (NRM) were 54% and 31%, respectively. Acute GVHD, grades 2–4, was noted in 35% of patients, with 13% of patients developing chronic extensive GVHD. Of note, patients transplanted with peripheral blood stem cells were twice as likely to develop chronic GVHD compared with patients who received bone marrow stem cells, confirming results of other randomized studies assessing the impact of stem cell source on transplant outcome.<sup>36,37</sup> 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.<sup>35</sup>

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.<sup>38</sup> 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.<sup>38</sup> 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.<sup>38</sup> After adjusting for differences in age and WBC count 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 non-significantly 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).<sup>38</sup>

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.<sup>31,39</sup> 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.<sup>39</sup> 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% versus 12%,  $p=.02$ ).<sup>31</sup> Furthermore, the advantage of a molecular response prior to 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.<sup>31</sup> This is in agreement with studies in the pediatric population where the level of residual disease prior to allo SCT correlates with outcome after SCT.<sup>40,41</sup>

**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 one to three years of follow-up.<sup>15,16,29,30</sup> As discussed previously, even prior to imatinib, patients in molecular remission at time of allo SCT had a longer DFS.<sup>31</sup> As a result, interim monotherapy with imatinib has been used to reduce the disease burden prior to allo SCT.<sup>42,43</sup> In a study by Lee et al, interim cycles of imatinib between induction and consolidation and between consolidation and allo SCT significantly improved the DFS and OS as compared to a historical group of patients treated with the same chemotherapy regimen but without imatinib.<sup>42,43</sup> The patients' *BCR-ABL/ABL* ratios declined by a median of 0.77 and 0.34 logs after each of the 2 cycles of imatinib.<sup>42,43</sup> 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.<sup>44</sup> Of note, thus far, the early results of studies incorporating imatinib into pre-transplant therapy have not demonstrated a clear survival difference between patients who receive an allo SCT for consolidation versus those who do not.<sup>15,16,29,30</sup> 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 et al had shown that Ph+ ALL patients who remained PCR positive after allo SCT had a significantly higher incidence of relapse than PCR-negative patients.<sup>45</sup> Therefore, use of imatinib in the post-transplant setting to eradicate minimal residual disease (MRD) has been investigated by several groups.<sup>46–48</sup> In the study by Wassmann et al, 27 Ph+ ALL patients received imatinib 400 mg daily upon detection of MRD post SCT.<sup>47</sup> 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 six 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% as compared to only 8% in patients remaining MRD positive after 12 months.<sup>47</sup> These data suggested the benefit of prophylactic administration of imatinib in the post allo SCT setting.<sup>48</sup> 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.<sup>49,50</sup>

As evident in the MRC UKALL XII/ECOG 2993 study, TRM overcomes any survival advantage for transplant in older patients. Since the incidence of ALL, particularly the Ph+ subtype, increases in adults over age 50 years, transplant approaches with reduced TRM such as non-myeloablative regimens are needed. Martino et al reported the largest series of non-myeloablative SCT in ALL.<sup>51</sup> They reported a TRM of 23%, OS of 31%, and disease progression of 49% at 2 years among 27 patients, with median age 55 years. A higher relapse rate was observed for patients transplanted with overt disease versus those transplanted in CR (60% versus 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 5–43%, the primary cause of failure being relapse (>50%).<sup>38,52–55</sup> 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 re-induction chemotherapy after relapse had a better outcome, with 5-year OS 47% versus 18%.<sup>55</sup> The authors suggested that patients who did not undergo salvage chemotherapy prior to SCT sustained less TRM leading ultimately to a better outcome.<sup>55</sup> Similarly, in the subset of patients who relapsed in the MRC ECOG/UKALL study, patients that were able to receive a matched sibling transplant had the best survival at 5 years (23%).<sup>56</sup> Factors predicting a better outcome were young age (OS 12% for patients <20 years-old versus 3% for patients greater than 50 years-old) and long duration of first remission (OS 11% for CR1 > 2 years versus 5% for CR1 < 2 years).<sup>56</sup>



With current induction regimens, only 5–10% 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 an HLA identical sibling can benefit if they proceed directly to allo SCT without undergoing a second attempt at induction therapy.<sup>57,58</sup> In the largest study 38 patients with ALL failing to achieve remission received HLA identical sibling transplants without re-induction.<sup>57</sup> Approximately 35% of these patients with refractory disease achieved long-term disease-free survival. A second study with 22 patients (5 with ALL) with refractory disease had a similar survival of 38% following HLA-matched sibling transplants.<sup>58</sup> Other studies suggest lower survival rates of 20% or less for these refractory patients.<sup>57,59</sup> 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 to 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 appears 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 quantitative PCR and transplanted at time of increasing *BCR-ABL* transcript levels. Alternatively, non-myeloablative 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 20–50% of patients transplanted in remission can achieve long-term disease control; relapse and engraftment remain significant issues.<sup>60</sup>

### Resistance to imatinib

Both acquired and intrinsic resistance to imatinib have 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).<sup>61,62</sup> 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.<sup>63–67</sup>

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.<sup>61,62,68</sup> 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 that alter the spatial conformation of the protein.<sup>61,62,69,70</sup> 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.<sup>71,72</sup> In one report E255K/V mutations were noted in 67% of patients but this was

not confirmed by the other study.<sup>71,72</sup> However, in these studies KD mutations occurring prior to 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.<sup>73</sup> In a follow-up study in a larger cohort of elderly patients enrolled into the GMALL randomized study,<sup>34</sup> 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.<sup>74</sup> 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. Remarkably, pre-existence 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.<sup>74</sup> This 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.<sup>74</sup> Jones et al have also recently reported the presence of KD mutations in the majority of patients with relapsed disease following imatinib therapy.<sup>75</sup> They 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 TKI compared to none of the patients who never received TKIs.<sup>75</sup> A limited spectrum of mutations, mostly Y253H, T315I, and F317L were noted and they were not present prior to 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.<sup>75,76</sup> Whether such acquired imatinib resistance is a result of outgrowth of small clones with mutant KD existing prior to 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.<sup>74,75</sup>

A new mechanism of resistance involves the expression of spliced isoforms of Ikaros (*IKZF1*). {Iacobucci, et al, Blood 2008} *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. {Cobb and Smale, Curr Top Microbiol Immunol 2005} The *Ik6* isoform, lacking all four N-terminal zinc fingers responsible for DNA-binding, was detected in 43 of 47 (91%) Ph+ ALL patients resistant to imatinib or dasatinib. {Iacobucci, et al, Blood 2008} 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. {Mishra, et al, Cancer Res 2006} 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 1 $\alpha$ , 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+ leukemias patients has fuelled the search for alternative, second generation inhibitors capable of overcoming the resistance.<sup>77-79</sup> 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 (Figure 1b).<sup>77</sup> The inhibition of other kinases particularly Src may be important in overcoming imatinib resistance particularly in patients with lymphoid leukemias where Src kinase activity may be important in the pathogenesis of the disease.<sup>80</sup> Dasatinib is active in vitro against all imatinib resistant BCR-ABL mutants with the notable exception of T315I.<sup>77</sup> It has demonstrated significant activity in phase I and II studies in Ph+ leukemias patients who were resistant to or intolerant of imatinib. Cortes et al reported the results of a phase II trial where patients with blast phase of CML who had failed imatinib, were treated with dasatinib 70 mg orally twice daily.<sup>81</sup> 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 et al conducted a phase II study of dasatinib in 36 Ph+ ALL patients after failing imatinib.<sup>82</sup> The median age of the patients was 46 years (range, 15 to 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 to those with no mutations.<sup>82</sup> More recent data has 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.<sup>83</sup> 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.<sup>85</sup>

Based on the significant activity of dasatinib against *BCR-ABL*, and impressive data in patients with relapsed disease, we have conducted a phase II study of combining the hyperCVAD regimen with dasatinib, administered at 50 mg orally twice daily for the first 14 days of each of the 8 induction/consolidation chemotherapy cycles, as frontline therapy.<sup>84</sup> Patients would then receive dasatinib continuously indefinitely with monthly cycles of prednisone and vincristine for the first 2 years. A lower dasatinib dose was chosen in order to avoid excessive myelosuppression when combined with intensive chemotherapy. Preliminary data has been recently reported demonstrating the feasibility of this regimen in both relapsed and previously untreated patients.<sup>84</sup> Among 28 patients with newly diagnosed disease (median age 52 years, range, 21-79 years), 26 (93%) achieved CR after 1 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.<sup>84</sup> Of note, *BCR-ABL* mutations were identified in 4 of the 5 relapsing patients (including 3 with T315I and 1 with F359V).<sup>84</sup>

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.<sup>86</sup> 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 one relapse and 3 deaths in CR were reported at a median follow up of 3.6 months.<sup>86</sup> 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.<sup>87</sup> Among the first 48 patients (median age, 54 years, range, 24–76), 34 were evaluable for response and a CR rate of 100% was reported with no deaths attributable to treatment.<sup>87</sup> With a median follow-up of 11 months, survival at 10 months was 81%. Nine patients had relapsed with 5 showing a T315I, 1 an E255K and 2 without mutations. Details of consolidation treatment were not provided.<sup>87</sup>

Existence of *BCR-ABL* mutations that may induce resistance to dasatinib is of significant concern.<sup>88</sup> 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.<sup>89</sup> 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 with respect increase of dasatinib IC50 to wild-type *BCR-ABL*.<sup>90</sup> As with imatinib-based therapy, at present, it is not clear whether these mutants exist pre-therapy and dasatinib treatment induces their overgrowth or 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 I and II trials. Of potential interest are agents with activity against the T315I mutants.

### Central nervous system (CNS) disease

CNS involvement is relatively 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.<sup>91,92</sup> However, with routine CNS-directed treatment, this risk has subsided to less than 10%. A number of recent studies have reported a relatively high incidence of isolated CNS relapse in Ph+ acute leukemias patients with generally unfavorable outcomes.<sup>93,94</sup> In the study by Leis et al 5 of 24 (21%) of 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.<sup>94</sup> Simultaneous plasma and CSF imatinib levels were measured in 4 subsequent patients and imatinib levels were noted to be 2 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.<sup>95</sup> These studies suggested that imatinib poorly penetrates the blood-brain barrier and underscore the need for adequate CNS directed therapy in patients receiving imatinib-based therapy. This may be, at least in part, 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 blood-brain barrier.<sup>96</sup> 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.<sup>96</sup> 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.<sup>96</sup> Furthermore, KD mutational analysis on the blasts from the CSF of 2 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.<sup>96</sup> Prospective studies evaluating the dasatinib CSF levels and its ability to decrease the incidence of CNS relapse are necessary to confirm these data.

### Future challenges in Ph+ ALL

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 upon 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 our therapeutic armamentarium against this disease.

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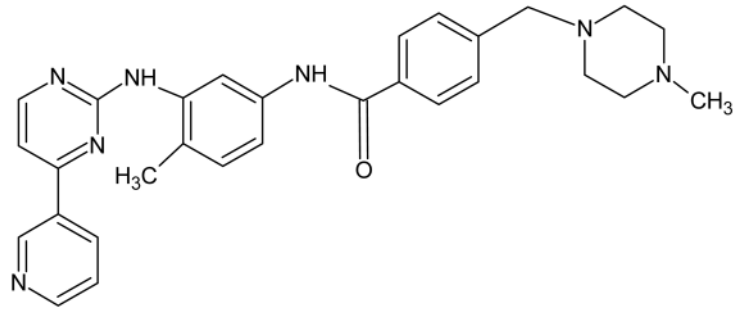
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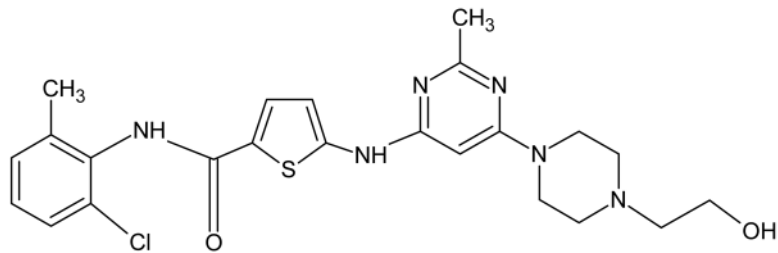
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(a)



(b)



**Figure 1.**  
(a) Imatinib, (b) Dasatinib

**Table 1**

## Selected chemotherapy trials in Ph+ ALL

Reference	Ph+, N (%)	CR %	Median EFS/CRD (months)	Median OS (months)
Bloomfield <sup>97</sup>	29 (17)	46	7	11
Gotz <sup>98</sup>	25	76	NA	8
Larsen <sup>99</sup>	30 (27)	70	7	11
GFCH <sup>100</sup>	127 (29)	59	5	NA
Secker-Walker <sup>101</sup>	40 (11)	83	13	11
Wetzler <sup>102</sup>	67 (29)	79	11	16
Faderl <sup>103</sup>	67 (13)	*55, 90	*8, 10.8	*11.3, 16.5
Dombret <sup>31</sup>	154	67		**19% at 3 years
Arico <sup>9</sup>	326	82	** 28% at 5 years	** 40% at 5 years
Schrappé <sup>10</sup>	61 (1)	75	** 38% at 5 years	** 49% at 5 years

GFCH: Groupe Francais de Cytogenetique Hematologique ; CR :complete remission ; EFS : event-free survival ; CRD : complété rémission duration ; OS : overall survival ;

\* results for the VAD and hyperCVAD regimens quoted, respectively;

\*\* estimated survival at X years

**Table 2**

Clinical trials incorporating imatinib into frontline chemotherapy for Ph+ ALL

Reference	N	Median age (range)	Imatinib and chemo schedule	CR %	Relapse %	EFS % (years)	Survival % (years)
Thomas <sup>15,26</sup>	45	51 (17–84)	Concurrent	93	22	68* (3)	55 (3)
Yanada <sup>16,28</sup>	80	48 (15–63)	Concurrent	96	26	51 (2)	58 (20)
Lee <sup>27</sup>	20	37 (15–67)	Concurrent	95	32	62 (2)	59 (2)
Lee <sup>32,43</sup>	29	36 (18–55)	Alternating	79	4	78 (3)	78 (3)
Wassmann <sup>29</sup>	45	41 (19–63)	Concurrent	*	*	61 (2)	43 (2)
	47	46 (21–65)	Alternating	*	*	52 (2)	36 (2)
de Labarthe <sup>30</sup>	45	45 (16–59)	Concurrent	96	19	51 (1.5)	65 (1.5)
Delannoy <sup>33</sup>	30	66 (58–78)	Alternating	72	60	58 (1)	66 (1)
Vignetti <sup>32</sup>	30	69 (61–83)	+Prednisone	100	48	48 (1)	74 (1)
Ottmann <sup>34</sup>	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)

CR: Complete remission; EFS: event-free survival;

\* CR duration reported

**Table 3**

## Reported potential mechanisms of resistance to imatinib

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<b>Mechanisms related to cellular uptake and retention of imatinib</b>
Increased MDR1 expression <sup>104</sup>
Reduced hOCT1 mediated influx <sup>67,105</sup>
Increased binding to $\alpha$ 1-acid glycoprotein-1 <sup>106</sup>
<b>BCR-ABL dependent mechanisms</b>
BCR-ABL over-expression <sup>61</sup>
BCR-ABL kinase domain mutations <sup>61,62</sup>
<b>BCR-ABL independent mechanisms</b>
Activation of alternate signaling pathways such as Src <sup>65</sup>
Clonal evolution <sup>107</sup>
<b>Miscellaneous</b>
Non-compliance
Stem cell quiescence <sup>108</sup>

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**Table 4**

Selected new agents being evaluated in Ph+ leukemias

<b>Drug</b>	<b>Mechanism of action</b>
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