Philadelphia Chromosome–positive Acute Lymphoblastic Leukemia: Impact of Imatinib Treatment on Remission Induction and Allogeneic Stem Cell Transplantation

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Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL) has been associated with the worst patient survival rates of the various acute leukemias. Imatinib mesylate is a novel therapeutic agent that targets the BCR-ABL tyrosine kinase, the molecular abnormality associated with Ph+ ALL. The combination of imatinib with chemotherapy has led to improved and durable treatment responses in adult patients with Ph+ ALL, including the elderly population. Hematopoietic stem cell transplantation has also integrated imatinib into its transplant strategies, with early data suggesting improved progression-free survival without clearly identifiable augmented toxicity. Second-generation tyrosine kinase inhibitors offer potentially even greater improvements on these excellent imatinib-associated outcomes. This review addresses the evolution of the management of Ph+ ALL and is intended to assist in the description of its new natural history.

Introduction
This review addresses the impact of imatinib (Gleevec; Novartis, East Hanover, NJ) treatment, upon the management of Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). We review incorporation of imatinib into various standard induction regimens both in young patients, for whom transplantation remains an option, and in the elderly, who might otherwise not have the ability to tolerate an allogeneic stem cell transplantation. Use of imatinib within the transplantation paradigm is also examined because, for Ph+ ALL, allogeneic hematopoietic stem cell transplantation (HSCT) remains the only proven curative therapy. The mechanisms of resistance to imatinib and the use of second-generation tyrosine kinase inhibitors are briefly discussed.

Historical Perspective
Ph+ ALL represents a small fraction of all patients with ALL. Only 6% of childhood ALL patients present with this cytogenetic translocation, although, in adults, the Ph chromosome rearrangement is the most frequent abnormality with an incidence estimated between 20% and 40% [1,2]. Significantly, in adults with Ph+ ALL, complete remission (CR) induction rates have been identified in 60% to 90%, using a variety of standard chemotherapeutic approaches with slightly lower remission induction rates, compared with adult patients with Ph-negative ALL [1–4]. Primary refractory disease was seen in 10% to 30% of cases. Molecular CR, as tested by reverse-transcription polymerase chain reaction (RT-PCR) in patients in CR after induction, was found in 27% of patients in the multicenter prospective LALA-94 (Leucemies Aigues Lymphoblastiques de l’Adulte-94) trial [2]. However, median remission duration historically has only approximated 10 months, with median survival of 11 months and an overall survival (OS) rate of 15% to 20% at 2 years. Based upon these statistics of limited remission duration and on the overall poor prognosis, Ph+ ALL has been considered as an indication for allogeneic HSCT in first CR from either a sibling or unrelated donor when allogeneic transplantation is considered feasible [5]. In the absence of a donor, survival was minimal.
Allogeneic HSCT from related and unrelated donors has traditionally been the only curative option in Ph+ ALL, with a 20% to 30% relapse rate, a 30% to 50% disease-free survival (DFS) rate, and a 30% to 50% OS rate [2,3,5–8]. Prognostic factors associated with better survival after allogeneic HSCT included total body irradiation in the conditioning regimen, chronic graft-versus-host disease (GvHD) [6,9,10], and lack of detection of the oncogene, BCR-ABL, by RT-PCR after transplantation during assessments of minimal residual disease [10–12]. The benefit of autologous stem cell transplantation has been minimal [2,3,13] except in rare patients with BCR-ABL negativity by RT-PCR at the time of transplantation [2].

In the past 5 years, major advances have occurred allowing for a complete reevaluation of the management of Ph+ ALL. These advances include the advent of reduced-intensity allogeneic HSCT, which has extended the application of allogeneic transplantation to older patients and to those who have comorbid clinical conditions, whether they be dormant infections or compromised organ function [14]. Second, and more importantly, imatinib has emerged as a critical agent in the management of disorders with the Ph chromosome. The Ph chromosome is a shortened chromosome 22 resulting from a reciprocal translocation between the lower arms of chromosomes 9 and 22. The consequence of this translocation is the fusion of the C-ABL oncogene from chromosome 9 with sequences of chromosome 22 identified as breakpoint cluster region “BCR.” The fused BCR-ABL gene results in a 210-kD protein (p210) or a shorter 190-kD protein (p190). The 210-kD product is the hallmark of chronic myeloid leukemia (CML), whereas the p190 is seen in 58% to 77% of patients with Ph+ ALL [1,2,15]. The chimeric BCR-ABL is a constitutively activated tyrosine kinase that has been shown to have many downstream cellular targets that ultimately lead to deregulated cellular proliferation and transformation [16]. Specifically, imatinib was designed as a small molecule inhibitor of the ATP binding site of tyrosine kinases that has shown high-affinity receptor binding to the deregulated BCR-ABL kinase oncogene and to other target kinases, including platelet-derived growth factor receptor (PDGFR) and C-KIT [17]. Binding of the molecule to the BCR-ABL oncogene leads to a blockade of the tyrosine kinase function and apoptosis of the cell. Based upon these excellent preclinical observations, clinical trials with imatinib were initiated in 1999 in CML.

Combined Imatinib Chemotherapy Induction Regimens: Next Step in Management of Ph+ ALL
The activity of imatinib monotherapy in relapsed Ph+ ALL and the in vitro synergy observed between imatinib and chemotherapy agents [24,25] logically led to the development of imatinib combination regimens in newly diagnosed Ph+ ALL patients (Table 1). Thomas et al. [26••] first reported the results of a multidrug chemotherapy regimen, hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, high-dose methotrexate, and cytarabine), and imatinib combination in a cohort of 20 patients, with a 100% hematologic response rate and 60% of patients gaining molecular CR. Imatinib was initially given at 400 mg/d for 14 days of each cycle. An update of these early results has been presented [27]. Imatinib was given at increased dosages of 600 mg/d for 14 days during the induction cycle and daily during all consolidation cycles, with a 24-month maintenance course. Forty-three patients have been treated, with a hematologic 94% CR rate after a median time of 21 days. Only 30% of patients have proceeded to allogeneic HSCT. With a median follow-up of 36 months, a relapse rate of only 10% was observed, with an OS rate of 79%.

The high response rates after concurrent administration of imatinib and chemotherapy have now been confirmed in several other phase II studies. The Japanese

Single-agent Imatinib: First Step in a New Paradigm for Management of Ph+ ALL
The original trials for imatinib included evaluation of its efficacy in patients with relapsed or refractory Ph+ ALL and advanced phases of CML. In a phase I study in patients with Ph+ ALL and blast-phase CML, single-agent imatinib at dosages of 300 to 1000 mg/d led to a 70% hematologic response and a 20% CR rate [18••]. Compared with myeloid blast-phase CML, lymphoid blast-phase CML and Ph+ ALL had lower response rates and a shorter duration of responses, with no long-term responders. The activity of imatinib in relapsed or refractory Ph+ ALL was confirmed in two additional phase II trials, with an overall 20% to 30% CR rate [19••,20]. In 56 patients with relapsed refractory Ph+ ALL, Ottmann et al. [19••] reported a 29% CR rate and a 17% rate of complete cytogenetic response, with a median response duration of 2.2 months and an OS duration of 4.9 months. An early medullary reduction in blasts to less than 5% by day 14 was predictive of hematologic CR [20]. In our institutional experience, the median time to peripheral blood response was 3 days during which time no evidence of tumor lysis syndrome was ever identified [21]. Eighty-nine percent of hematologic CR patients were shown to have gained a complete cytogenetic response, and 28% had a negative RT-PCR result for BCR-ABL on at least one occasion, suggesting at least a three-log reduction of the disease burden [22]. However, these responses were brief, with most of these advanced patients progressing within the ensuing months with no long remissions identified unless they had the opportunity to undergo allogeneic HSCT in complete hematologic response [23].
Adult Leukemia Study Group recently presented updated results of its experience in 80 patients [28•]. Imatinib was started on day 8 of induction at 600 mg/d and was given continuously except during the first consolidation cycle. A total of 80 patients were treated, with a CR rate of 96%, a molecular CR rate of 50%, and an OS rate of 76% at 2 years. A 25% relapse rate was observed, and in that group, median CR duration was only 5.2 months. DFS and OS were superior to the results in historical controls for nontransplanted patients (Fig. 1). A recent multicenter study from Korea combining the “Linker” regimen [29] with continuous imatinib also demonstrated a 95% CR rate, a 50% molecular CR rate, and a relapse rate of 31% [30]. The GMALL (German Multicenter Trials for Adult ALL; MDACC—M.D. Anderson Cancer Center; OS—overall survival; PETHEMA—Hematology Division, Grupo Espanol de MM (multiple myeloma); Ph—Philadelphia chromosome).

### Table 1. Studies with imatinib in combination with standard induction chemotherapy in newly diagnosed adult Ph+ ALL

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>CR, %</th>
<th>Molecular CR, %</th>
<th>EFS, % (y)</th>
<th>Relapse, %</th>
<th>OS, % (y)</th>
<th>Transplant, %</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas et al. [26••]</td>
<td>20</td>
<td>93</td>
<td>60</td>
<td>84 (2)</td>
<td>—</td>
<td>64 (2)</td>
<td>50</td>
<td>The original trial of the MDACC, with imatinib given at 400 mg/d for 14 days with each chemotherapy cycle</td>
</tr>
<tr>
<td>Thomas et al. [27]</td>
<td>43</td>
<td>94</td>
<td>NA</td>
<td>—</td>
<td>10</td>
<td>79 (3)</td>
<td>30</td>
<td>Updated series of the MDACC trial; increased doses of imatinib given during induction for 14 days and continuously during consolidations</td>
</tr>
<tr>
<td>Yanada et al. [28•]</td>
<td>80</td>
<td>96</td>
<td>79</td>
<td>60 (1)</td>
<td>25.9</td>
<td>76.1 (2)</td>
<td>63</td>
<td>The Japanese Adult Leukemia Study Group; imatinib was given during induction and after the second consolidation</td>
</tr>
<tr>
<td>Lee et al. [30]</td>
<td>20</td>
<td>95</td>
<td>50</td>
<td>—</td>
<td>31.6</td>
<td>—</td>
<td>85</td>
<td>Imatinib given during induction at 600 mg/d and at 400 mg/d during consolidation for 14 days, then without interruption</td>
</tr>
<tr>
<td>Lee et al. [36••]</td>
<td>29</td>
<td>79</td>
<td>24</td>
<td>78.1 (3)</td>
<td>4</td>
<td>78.1 (3)</td>
<td>86</td>
<td>Alternating standard chemotherapy and imatinib, providing a bridge to transplant</td>
</tr>
<tr>
<td>Ottmann et al. [31]</td>
<td>46</td>
<td>96</td>
<td>50</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>GMALL study included 2 patient cohorts; cohort 1 received imatinib concurrently with induction, and cohort 2 after achievement of CR; only cohort 1 patients are included in this table</td>
</tr>
<tr>
<td>Ribera et al. [32]</td>
<td>19</td>
<td>89</td>
<td>50</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>PETHEMA study; imatinib given at 400 mg/d starting at induction</td>
</tr>
</tbody>
</table>

ALL—acute lymphoblastic leukemia; CR—complete remission; EFS—event-free survival; GMALL—German Multicenter Trials for Adult ALL; MDACC—M.D. Anderson Cancer Center; OS—overall survival; PETHEMA—Hematology Division, Grupo Espanol de MM (multiple myeloma); Ph—Philadelphia chromosome.
Combination chemotherapy and imatinib is also being studied in advanced Ph+ ALL. In relapsed or resistant disease, Rea et al. [35] recently described a novel regimen called DIV, combining imatinib 800 mg/d only with vincristine and dexamethasone. All 18 patients had relapsed or refractory disease, three patients had been previously exposed to imatinib, and two patients had failed previous allogeneic HSCT. A hematologic CR was observed in 94% of patients, with a major cytogenetic response in 80% of patients and 10% molecular CR. After a median follow-up of 256 days, 64% of patients remain in CR. The toxicity of the regimen was mainly infectious.

The optimal timing and dosing of imatinib administration with induction regimens has not yet been firmly established. The current conclusions from studies that utilize imatinib early and concurrently with chemotherapy reveal CR rates greater than or equal to 95% and molecular CR rates of 50% [27,28•,30–32], whereas a single study administering imatinib alternating with chemotherapy reported a slightly reduced CR rate of 79% and a molecular CR rate of 27% [36••], suggesting that early administration of imatinib may lead to higher response rates. The dose of imatinib given in combination has progressively increased to 600 mg/d in recent studies. A dosage of 800 mg/d was administered with a high-dose cytarabine (Ara-C) and mitoxantrone chemotherapy combination (HAM) in a study by the French-Belgian-Swiss GRAALL (Group for Research in Adult Acute Lymphoblastic Leukemia) but was associated with significant toxicity [37].

Taken together, imatinib and chemotherapy combinations show a remarkable increase in CR achievement and in response duration, compared with the remission induction and consolidation regimens of the prior two decades. If these data are substantiated with long-term follow-up, it is anticipated that remission induction treatment with BCR-ABL kinase inhibitors will become standard. However, follow-up in all of these studies is short, with no data currently available to support the contention that allogeneic HSCT need no longer be pursued.

### Transplantation

The acceptable tolerance, high response rates, and increased response duration to imatinib and standard chemotherapy combinations have led to questions about the feasibility of allogeneic HSCT in imatinib-treated Ph+ ALL patients. The majority of early studies reporting small cohorts of transplanted patients did not observe excessive toxicity or increased transplant-related mortality (TRM) in patients pretreated with imatinib [23,30,38], even in those with refractory/relapsed Ph+ ALL. Only a preliminary report from a single center of 21 patients with CML and Ph+ ALL reported increased toxicity and mortality in imatinib-exposed patients, with a 72% TRM rate and 12% survival in the imatinib group, versus 35% and 55%, respectively, in patients who had not been exposed to imatinib [39]. Most of these patients had received a busulfan-containing conditioning regimen, which was also associated with cardiac toxicity in a case
A recent retrospective analysis of 91 patients with advanced Ph+ leukemias, including 21 with Ph+ ALL, treated at Oregon Health and Sciences University and various EBMT (European Group for Blood and Marrow Transplant) centers, confirmed the lack of a negative impact of imatinib exposure on transplant outcome and that acceptable outcomes could be obtained, primarily for those with disease control prior to allogeneic HSCT [41].

One of the first prospective studies, which evaluated allogeneic HSCT in 29 imatinib-treated patients, was reported by Lee et al. [36••]. Notable findings that were identified within this report include that the proportion of patients proceeding to transplant increased significantly, as 86% of imatinib-treated patients could be transplanted in first CR, versus only 55% in a historical control cohort from the same group. Second, the overall toxicity and TRM rate did not differ significantly from those of pre-imatinib patients. Finally, DFS and OS at 24 months were both 78.1%, versus 38.7% in the historical control cohort immediately transplanted before the availability of imatinib (<0.001) (Fig. 2).

Minimal residual detection by RT-PCR for BCR-ABL showed an increase in complete molecular response from 27% before HSCT to 73% after HSCT. In another series, from the Japanese Adult Leukemia Study Group, allogeneic HSCT was performed in 61% of patients (49 patients total), including 49% in first CR [28•]. Again, no excessive toxicity was observed in comparison with results in historical controls. DFS and OS rates at 1 year were 79% and 73%, respectively, but only DFS was statistically superior to results in allotransplanted patients treated without imatinib.

The possibility of posttransplantation imatinib administration was addressed in a brief report by Wassmann et al. [23], including results from 27 allografted patients with evidence of post-HSCT minimal residual disease by RT-PCR. These patients received imatinib at 400 to 600 mg/d starting at a median of 4.4 months after transplantation. Fifty-two percent of the patients reached a molecular CR after a median time of 1.5 months. Early molecular responders, defined as patients achieving a molecular CR within 3 months of starting imatinib, had a 54% DFS and 80% OS at 2 years. Post-HSCT imatinib was well tolerated. No grade 4 hematologic and no de novo GvHD disease were observed.

Current opinion is that reduced-intensity allogeneic transplantation, using even moderately intense regimens, may prove to have limited benefit in patients with advanced ALL, with the expectation that there will be increased relapse rates [41]. The largest series in high-risk ALL patients have shown high relapse rates (58%) and significant TRM (24%), with an estimated 3-year leukemia-free survival rate of 18% [42]. Small series also support that reduced-intensity transplant may benefit high-risk ALL patients, but mostly when they are transplanted early in the disease course [43–45]. The 2-year survival rate of Ph+ ALL patients transplanted in these series was less than 20%. Currently, with the proven benefit of imatinib in the pretransplant and posttransplant settings, Ph+ ALL may represent a unique circumstance. Imatinib in combination with chemotherapy leads to the rapid acquisition of a minimal residual disease state [26••,28•,30], allowing the establishment of the allogeneic graft-versus-leukemia effect observed in ALL to take place [46]. In conjunction with the efficacy of imatinib in the treatment of elderly Ph+ ALL patients, it is logical to anticipate that these strategies will be reported in the near future.

Finally, autologous HSCT has been reportedly not better than chemotherapy for treatment of Ph+ ALL [5], except...
in the rare cases in which PCR-negative states could be achieved [2]. Again, the availability of imatinib will allow new clinical investigations to emerge, analyzing the feasibility and efficacy of these strategies. The US Cancer and Leukemia Group B (CALGB) and the European GRAALL studies are currently investigating these approaches, and scattered anecdotal reports are emerging [47].

Overall, these results show that imatinib administration prior to transplant has no negative impact on the outcome of the transplantation and that imatinib can be safely administered after transplant, although the benefit of post-transplant administration is still under investigation. All of these transplantation data suggest that, from this time forward, it will be difficult to imagine ever pursuing allogeneic HSCT in Ph+ ALL patients in the absence of imatinib or other second-generation tyrosine kinase inhibitors.

Elderly Patients
The prognosis of ALL in elderly patients is extremely poor, irrespective of the presence of the Ph chromosome [48–50]. Overall, a CR rate of 59% is observed, with an approximately 22% treatment-related death rate and a median survival of 10 months [50]. The activity of monotherapy with imatinib in relapsed Ph+ ALL prompted several groups to test this agent in small phase II studies, which have been reported only in abstract form but appear very promising (Table 2). The German GMALL group randomized 49 elderly patients (median age, 68 years) to receive imatinib at 600 mg/d, followed by consolidation chemotherapy, or to receive standard induction therapy followed by imatinib. CR was reached in 96% of patients randomized to imatinib versus 61% in the chemotherapy arm [51]. Severe infections were observed in 12% of patients randomized to the imatinib arm and 57% of patients receiving standard induction. There were no toxic deaths during induction in the imatinib arm versus two deaths in the chemotherapy arm. At 18 months, the estimated DFS and OS rates of all available patients were 27% and 43%, respectively. In a study by the Gruppo Italiano Malattie Ematologiche dell’Adulto (GIMEMA), 12 patients older than 61 years were treated with imatinib, 600 mg/d, and prednisone for 30 days, followed by imatinib monotherapy [34]. Eleven patients (92%) achieved CR. With a median follow-up of 7 months, eight patients (66%) were in continuous CR. The European GRAALL Intergroup used a different approach in 29 patients older than 55 years [52]. Treatment consisted of a standard induction, followed by imatinib alternating with steroid pulses. Seventy-one percent of patients reached CR after induction, with an additional 17% reaching CR after imatinib, for a total CR rate of 89%. The projected OS at 1 year was 71%, significantly higher than 43% OS in the historical group. Finally, in a recent single-institution report of a retrospective analysis of elderly patients with ALL, Brandwein et al. [48] observed an improvement in the OS of elderly Ph+ ALL patients starting in 2000, following the introduction of imatinib [48]. Although these studies are still preliminary and involve limited numbers of patients, they suggest that the management of Ph+ ALL in the elderly population will be improved by the addition of imatinib.

Central Nervous System Disease
In Ph+ ALL patients treated with single-agent imatinib, a 12% to 20% incidence of central nervous system involvement has been detected. Simultaneous plasma and cerebral spinal fluid (CSF) imatinib levels have shown that only 1% to 2% of imatinib crosses the blood-brain barrier and that the imatinib levels achieved in the CSF were significantly below the concentration required for BCR-ABL inhibition. These results suggest that these patients should routinely and rapidly receive intrathecal prophylaxis [53,54], particularly in the situations in which imatinib induction is planned, in the absence of other agents that might cross the blood-brain barrier.

Mechanisms of Resistance to Imatinib
The mechanisms of resistance to imatinib have been extensively studied in CML and include the acquisition of mutations in the kinase domain of ABL in 50% to 90% and BCR-ABL amplification in 10% of patients with newly acquired imatinib resistance [55]. BCR-ABL tyrosine kinase mutations are observed in Ph+ ALL, but the
available information on their frequency is still limited, based on the small number of case studies so far. In one early study, Hofmann et al. [56] detected primarily the E255K mutation in six of nine Ph+ ALL cases with secondary resistance to imatinib. In a large series of 94 Ph+ ALL patients who developed resistance to imatinib, Pfeifer et al. [57] detected BCR-ABL kinase domain mutations in 55%. The most frequent mutations were E255K (38%), Y253F/H (22%), and T315I (20%). Twenty-five percent of patients had more than one mutation.

The development of the second-generation tyrosine kinase inhibitors dasatinib and AMN107 is promising in the management of imatinib-refractory Ph+ ALL. Dasatinib is a very attractive compound in Ph+ ALL because, in addition to inhibiting BCR-ABL with greater potency than imatinib, it is also a selective inhibitor of SRC kinases, which have been implicated in the pathogenesis of Ph+ ALL [58]. In a phase II trial testing single-agent dasatinib in imatinib-refractory Ph+ ALL patients, dasatinib induced a major hematologic response in 60% of patients [59], indicating that either the high-dose chemoradiotherapy or the eradication of imatinib-refractory CML and Ph+ ALL can still be successful in adults: significant roles of total body irradiation and chronic graft-versus-host disease. Bone Marrow Transplant 2005, 36:867–872.

Conclusions
The addition of imatinib to induction regimens has led to a remarkable increase in CR achievement and in response duration in Ph+ ALL in adult and elderly patients. However, the durability of these responses needs to be defined. Patients should still routinely be referred for allogeneic HSCT when donors are available and when the transplant process is deemed clinically appropriate. Future studies are required to provide information on the optimal combination of imatinib and chemotherapy and to determine the potential impact of imatinib on autologous HSCT and reduced-intensity allogeneic HSCT. The characterization of the molecular mechanisms involved in imatinib resistance and the development of second-generation BCR-ABL inhibitors are expected to further improve the management of Ph+ ALL.

References and Recommended Reading
Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance


One of the first studies documenting the activity of single-agent imatinib in refractory/refractory+ ALL (See [19••]).


One of the first studies documenting the activity of single-agent imatinib in refractory/refractory+ ALL (See [18••]).


The largest study showing the activity of a combined imatinib and standard induction regimen in newly diagnosed Ph+ ALL.


The first study showing the impact of imatinib on allogeneic HSCT and minimal residual disease detection in newly diagnosed Ph+ ALL.


