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Role of Tyrosine Kinase Inhibitors in the Management of Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia

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Abstract The Philadelphia chromosome is the most common cytogenetic abnormality found in adult patients diagnosed with acute lymphoblastic leukemia. The result of this abnormality is the BCR-ABL protein, a constitutively active kinase involved in cell signaling and survival. When managed with multiagent chemotherapy regimens alone, patients have traditionally had an inferior outcome in terms of remission duration and overall survival when compared with patients who are Philadelphia chromosome–negative. Small-molecule tyrosine kinase inhibitors, such as imatinib and dasatinib, directly inhibit the BCR-ABL kinase, offering a targeted approach as a therapeutic option. As a result of several clinical trials with adequate follow-up, imatinib combined with chemotherapy represents the current standard of care for patients with newly diagnosed disease. Allogeneic stem cell transplantation has previously been the only modality to offer the potential for a cure, and it still should be considered for all patients deemed able to tolerate such an intervention. Second-generation tyrosine kinase inhibitors, such as dasatinib, may further improve the outcome in these patients. The role of molecular monitoring and the use of tyrosine kinase inhibitors after stem cell transplantation are areas of active investigation, and the results of ongoing trials will help to clarify the optimal management of these patients.

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Introduction

The Philadelphia chromosome (Ph) is the product of a balanced translocation between the long arms of chromosomes 9 and 22, first discovered nearly four decades ago [1]. The translocation results in an oncogenic fusion gene capable of producing a constitutively active tyrosine kinase protein. In adult patients with acute lymphoblastic leukemia (ALL), Ph represents the most common cytogenetic abnormality, occurring in 20% to 30% of patients with newly diagnosed ALL [2]. Compared with their Philadelphia chromosome–negative counterparts, patients with Ph+ ALL traditionally have an inferior outcome in terms of disease-free survival (DFS) and overall survival (OS) [3, 4]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has long been regarded as the only intervention that potentially can lead to long-term leukemia-free survival in patients who achieve a complete remission (CR) after chemotherapy [5]. When small-molecule tyrosine kinase inhibitors (TKIs) are incorporated into treatment regimens, patients have superior CR and DFS rates and a higher likelihood of proceeding to allo-HSCT [6, 7]. In this review, we aim to update the readers on the current role of TKIs for the management of Ph+ ALL, focusing on data published or presented during the past 12 months. However, historical perspectives will be necessary to provide proper context. It is very important to note that the available studies have generally involved small numbers of patients, and the manner in which TKIs were

employed has varied considerably. Other major factors that must be considered in interpreting the literature include patient age at diagnosis, the percentage of patients receiving allo-HSCT, and the duration of follow-up when various outcomes are reported.

Background

Imatinib mesylate, a specific BCR-ABL kinase inhibitor, has revolutionized the treatment of chronic myeloid leukemia (CML), a hematologic malignancy known to be driven by the presence of the Philadelphia chromosome [8]. Indeed, most patients with CML now live essentially leukemia-free for extended periods, with no evidence of the Philadelphia chromosome on karyotypic analysis [9]. These results in CML led to interest in the use of imatinib in other malignancies harboring this genetic abnormality, such as Ph+ ALL [10]. Ottmann and colleagues initially studied imatinib as a single agent in patients with relapsed or refractory Ph+ ALL [11]. Although the drug was proven to be highly active, responses were followed rapidly by the development of resistance and subsequent progression of the leukemia. Based on data showing synergy between imatinib and cytotoxic chemotherapy [12], multiple investigators took the next logical step, which involved adding imatinib to conventional regimens used to treat Ph+ ALL. At present, it is well accepted that TKI therapy should be included in the front-line treatment program for all patients with this disease.

Imatinib

Several groups have now presented or published relatively mature data on their experience incorporating imatinib into treatment programs for Ph+ ALL (Table 1). Thomas and colleagues from the M. D. Anderson Cancer Center added imatinib to the hyper-CVAD regimen (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with methotrexate and high-dose cytarabine) in newly diagnosed or minimally treated patients [13, 14]. The final regimen called for imatinib to be dosed at 600 mg once daily for 14 days during induction, then 600 mg once daily continuously during the consolidation cycles. After consolidation, the dose of imatinib was increased to 800 mg daily and it was administered as maintenance along with monthly vincristine and corticosteroids. The analysis included 54 patients, with 93% achieving a CR. OS at 3 years was 54%, compared with 15% for patients who received the same chemotherapy regimen without imatinib. Similarly, other investigators have documented a very high CR rate and improved DFS with the addition of a TKI to standard chemotherapy. The Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) recently presented long-term follow-up on 45 patients who received imatinib with chemotherapy in a stratified manner, based on their early response to corticosteroids and chemotherapy [15]. Four-year OS in these patients was estimated to be 52%, which was highly favorable when compared with the rate for a historical group of patients treated in the pre-imatinib era.

Table 1 Major clinical trials involving tyrosine kinase inhibitors (TKIs) for Philadelphia chromosome–positive ALL

Study	*N*	Median age, *y*	TKI strategy	CR, *%*	AlloHSCT, *%*	OS, *%*
MDACC (imatinib) [14]	54	51	Imatinib 600 mg daily with HyperCVAD[a]	93	30	54 (3-year)
CSTIBES02 [16]	30	44	Imatinib 400 mg daily continuously with chemotherapy	90	53	30 (4-year)
NILG [17]	59	45	Imatinib 600 mg daily×7 days starting 3 days prior to each chemotherapy	91	63	38 (5-year predicted)
GMALL [19]	335	43	Imatinib 600 mg daily given according to three different schedules[b]	88	66	40 (4-year)
MRC/ECOG [20•]	175	NR	Imatinib 600 mg daily given starting at two different time points[c]	92	44	42 (3-year)
MDACC (dasatinib) [40•]	35	53	Dasatinib 100 mg daily with HyperCVAD[d]	94	11	64 (estimated 2-year)

ALL acute lymphoblastic leukemia, *AlloHSCT* allogeneic hematopoietic stem cell transplantation, *GMALL* German Multicenter Study Group for Adult Leukemia, *MDACC* M.D. Anderson Cancer Center, *MRC/ECOG* Medical Research Council/Eastern Cooperative Oncology Group, *NILG* North Italian Leukemia Group, *y* year

[a] HyperCVAD = Fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine (imatinib given on days 1–14 during induction, then continuously with courses 2–8; dose of imatinib increased to 800 mg during maintenance)

[b] *Cohort 1:* Imatinib between induction and consolidation 1; *Cohort 2:* Imatinib given during second half of induction and continued through stem cell transplantation; *Cohort 3:* Imatinib initiated with the start of induction and continued through stem cell transplantation

[c] *Cohort 1:* Imatinib as a consolidation after two phases of induction; *Cohort 2:* Imatinib started with the second phase of induction

[d] HyperCVAD = Fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine (dasatinib given on days 1–14 during induction and consolidation courses; dasatinib 100 mg daily administered as part of maintenance therapy)

Final results of the CSTIBES02 trial conducted by the Programa Espanol de Tratmiento en Hematologia (PETHEMA) and Grupo Espanol de Transplante Hemopoyetico (GETH) were recently published [16]. Imatinib was added to standard chemotherapy and administered in a continuous manner at a dose of 400 mg once daily. The goal for patients with a matched sibling donor was to proceed to allo-HSCT after achieving CR. The median age of patients was 43 years, but some patients were older than 60 years of age. Overall, 27 (90%) of 30 patients enrolled obtained CR, and 16 patients were able to undergo allo-SCT. With a median follow up of 4 years, the probabilities of both OS and leukemia-free survival were 30% [16].

The Northern Italy Leukemia Group (NILG) recently reported the results of the Ph+ arm of Protocol 09/00, which included 59 patients who received TKI-based therapy; these patients were compared with 35 patients who received chemotherapy only in the pre-imatinib era [17]. The group designed the tested regimen based on imatinib's potential to sensitize leukemia cells to chemotherapy [18]. Imatinib was given for 7 days in a pulsed manner, commencing 3 days before each round of chemotherapy. All patients who were eligible proceeded to allo-HSCT, and more patients in the imatinib group realized this goal (63% vs 39%, P=0.041). After a median follow-up of 5 years, patients in the imatinib group had a significantly lower rate of relapse (P=0.005) and an improved OS probability compared with a control group who did not receive imatinib (0.38 vs 0.23, P=0.009). The authors have since modified their strategy for adding imatinib to chemotherapy [17].

The optimal schedule for using imatinib (e.g., when to introduce the drug, what to combine it with) in patients with Ph+ ALL has remained an open issue, as encouraging results have been reported with both concurrent and alternating strategies. Conceivably, if identical outcomes were possible with less TKI therapy, patients could be spared unnecessary toxicity and expense. However, recently presented data appear to indicate a substantial long-term benefit for patients who receive TKIs earlier and in a more prolonged fashion, as opposed to using an intermittent or alternating strategy [19, 20•]. Continuous administration of imatinib has also improved the outcome for pediatric patients with Ph+ ALL [21].

The German Multicenter Study Group for Adult ALL (GMALL) previously reported that administering imatinib and chemotherapy simultaneously in a prospective study had a greater antileukemic effect than an alternating schedule [22]. The same group recently reported on the long-term outcome of patients enrolled on three different schedules of imatinib therapy [19]. Three different cohorts were given imatinib as follows: 600 mg daily as a single agent between induction and first consolidation (as well as after the first consolidation course, n=51), 600 mg daily starting during the second half of induction and continuing until allo-HSCT (n=105), or 600 mg daily starting immediately with the start of induction and continued until allo-HSCT (n=179). At 4 years, OS seemed to improve with earlier and more prolonged administration of imatinib (31% vs 40% vs 50%; P values not provided) [19].

The Ph+ arm of the Medical Research Council (MRC) UKALL12/ECOG2993 trial is the largest single study of patients with Ph+ ALL to date [20•]. The investigators in this multinational, prospective study have recently presented data on three cohorts of patients treated since 1993: Cohort 1 represents patients treated in the "pre-imatinib" era, Cohort 2 received imatinib as a consolidation course, and Cohort 3 were started on imatinib early, with phase two of the induction regimen. With 3 years of follow-up, there was a clear advantage favoring the patients who received imatinib early in terms of OS, event-free survival (EFS), and relapse-free survival (RFS). It was also demonstrated that the "early" imatinib group had superior outcome when compared to the "late" imatinib group (OS at 3 years, 48% vs 34%, P=0.05). Based on the observations of the aforementioned trials, it can now be recommended that TKI therapy should be started as soon as PH+ status is confirmed and should be continued throughout the treatment course.

The improvement in outcome with early and protracted administration of TKI therapy may be a consequence of the depth of response attainable with such a strategy. Monitoring minimal residual disease (MRD) has become increasingly important in pediatric and adult patients with ALL [23]. In a recent study by the group at St. Jude Children's Research Hospital, detection of MRD was the only adverse predictor of outcome aside from having central nervous system involvement at diagnosis [24]. For Ph+ ALL, real-time polymerase chain reaction (PCR), which can detect the low-level presence of BCR-ABL transcripts, has been used for MRD monitoring [25]. Investigators from Germany have published their experience in using imatinib after transplantation in patients who become PCR-positive [26]. Indeed, 92% of patients failing to achieve molecular remission shortly after the start of TKI therapy experienced relapse. Conversely, achieving PCR negative status early after starting imatinib predicted a far better outcome, with long-term remissions noted. Other studies have demonstrated conflicting results regarding the correlation of a reduction in BCR-ABL transcripts and patient outcome [27, 28]. The group from the M.D. Anderson Cancer Center recently presented data on the dynamics of molecular response in patients being treated with imatinib or dasatinib for Ph+ ALL as front-line therapy [29]. At 3 months and 6 months, more patients in the dasatinib group achieved molecular CR. Long-term follow up from these studies will be necessary to

determine whether achieving a rapid molecular remission will translate into meaningful clinical benefits. Flow cytometry is another powerful method used to detect MRD in ALL patients [23]. In a study conducted by the Polish Adult Leukemia Study Group, MRD positivity after induction chemotherapy was highly predictive of relapse in a group of patients with Ph- ALL [30].

A substantial number of patients with Ph+ ALL eventually progress despite treatment with a regimen containing imatinib [31]. Mutations in the kinase domain of the BCR-ABL protein play a substantial role in the development of resistance to imatinib and other TKIs [32]. Low levels of mutant BCR-ABL clones are frequently detected in patients upon diagnosis, but they do not appear to influence the initial response to TKI therapy [33]. Kinase domain mutations impair the binding of TKIs at their primary site of action, leading to drug resistance. This underscores the need for alternative treatments that may avert these mutations or may act via different mechanisms. Additionally, it has previously been noted that other pathways, such as the SRC kinase pathway, are necessary for the propagation of Ph+ ALL [34].

Second-Generation Tyrosine Kinase Inhibitors

The propensity for patients to develop intolerance or resistance to imatinib created the need for second-generation inhibitors that may overcome these problems [35, 36]. Dasatinib is a dual SRC and ABL kinase inhibitor that inhibits the BCR-ABL protein at 325 times the potency of imatinib [35]. Dasatinib is active in vitro against nearly all reported mutations, with the important exception of T315I [37].

Dasatinib was initially studied in patients with Ph+ ALL who were deemed imatinib-resistant or intolerant [31]. Patients (42% of whom had prior SCT) were started on dasatinib 70 mg twice daily as a single agent and continued until disease progression or unacceptable toxicity. Of 36 patients receiving study medication, 58% attained a complete cytogenetic response, establishing marked activity in a group of patients without many viable therapeutic alternatives. The median duration of progression-free survival was 3.3 months.

A recent international randomized phase 3 dose-optimization study compared the safety and efficacy of two different doses of dasatinib in Ph+ ALL [38]. In this study, 84 patients in whom imatinib had failed were randomly assigned to receive dasatinib at a dosage of 140 mg once daily or 70 mg twice daily, and they were observed for 2 years. Complete hematologic response, complete cytogenetic response, progression-free survival, and OS did not statistically differ between the two groups. However, there were fewer instances of pleural effusions in the once-daily group (grades 3–4, 5% vs 14%). Based on the results of this study, dasatinib is now approved in the United States for use in patients with Ph+ ALL at a dose of 140 mg daily as a single agent [39].

Though the responses in these studies are encouraging, it is important to note that they were relatively brief and occurred in a fairly young patient population. Given the results of dasatinib alone as salvage therapy, as well as its distinct pharmacologic properties, it became important to examine the drug's potential role as a front-line option when combined with conventional chemotherapy programs. The group from the M. D. Anderson Cancer Center treated 35 patients with newly diagnosed Ph+ ALL using a combination of the hyper-CVAD regimen (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and high-dose cytarabine) and dasatinib [40•]. During induction and consolidation, dasatinib was administered at a dose of 50 mg twice daily (or 100 mg once daily after the protocol was amended) during the first 14 days of each cycle of intensive chemotherapy (eight courses intended). Subsequently, patients went on to receive dasatinib 100 mg continuously as part of a maintenance program, together with monthly vincristine and prednisone. The response to therapy was favorable, with 94% of patients achieving CR. With a median follow-up of 14 months, estimated 2-year OS was 64%. Remarkably, only 4 of 36 patients went on to receive allo-HSCT, but overall outcomes appeared comparable to other trials of Ph+ ALL employing TKIs. Though tolerable, the regimen of hyper-CVAD plus dasatinib was associated with pleural effusions and hemorrhagic events in a number of patients, but these effects were generally reversible.

The data accumulating for imatinib and dasatinib are highly encouraging, but relapses do occur and additional therapeutic options remain necessary. Nilotinib is a BCR-ABL inhibitor that is more potent and selective than imatinib [41]. Like dasatinib, this agent also retains a high degree of activity against most of the relevant mutations conferring imatinib resistance. Importantly, this activity does not include T315I and several other mutations [37]. Nilotinib was evaluated in a dose-escalation study, which included several patients with relapsed or refractory Ph+ ALL [42]. The drug demonstrated a modest degree of activity. Recently, a large, phase 3, randomized trial found nilotinib to be superior to imatinib in treating chronic-phase CML [43]. Nilotinib also was used after SCT in a patient with MRD that persisted despite imatinib and dasatinib therapy [44]. After 9 months of therapy, the patient remained in remission and became PCR negative. Nilotinib at a dose of 400 mg twice daily has also been combined with the hyper-CVAD program and used as a front-line

regimen in a very small number of patients [45]. In this pilot study, four patients with Ph+ ALL were treated, and all of them achieved CR. The authors stated that a larger, phase 2 trial is being designed.

Other Kinase Inhibitors

Relapse remains a major concern in patients with Ph+ ALL. Many patients have the potential to be exposed to multiple TKIs, introducing the risk of the development of treatment-emergent kinase domain mutations resistant to all currently approved TKIs, including the "pan-resistant" T315I mutation [46]. Several additional kinase inhibitors are in various stages of clinical development, including ponatinib (AP24534), bosutinib, INNO-406, XL228, and DCC-2036 [47].

Ponatinib (formerly AP24534) is a rationally designed multikinase inhibitor that has the ability to inhibit BCR-ABL in the presence of a T315I mutation [48]. Data from a phase 1 trial were recently presented; this trial included mostly patients with CML that had failed multiple TKIs and harbored kinase domain mutations [49]. Nine patients with advanced Ph+ leukemia, including three with Ph+ ALL, were also treated in this study. Among these, two patients (20%) achieved a major cytogenetic response. Dose-limiting toxicities included pancreatitis and rash. Phase 2 trials of this agent are under way, and studies evaluating ponatinib in combination with chemotherapy are likely to be warranted.

Stem Cell Transplantation

Allo-HSCT has been long regarded as the only potential curative option for patients with Ph+ ALL [5]. In the pre-imatinib era, OS was significantly improved for patients who were able to receive allo-HSCT in first CR (3-year estimated OS, 37% vs 12%; P=0.02) [50]. Perhaps one of the most evident benefits offered by the addition of TKIs to chemotherapy has been the increased likelihood of patients proceeding to transplantation [51]. Indeed, the rate of allo-HSCT in the UKALLXII/ECOG2993 trial improved with the addition of imatinib (28% in the pre-imatinib era, compared with 44% for patients receiving any imatinib on protocol) [20•].

In the imatinib era, allo-HSCT in first CR still seems to play a major role in long-term leukemia-free survival. In the GMALL study, patients who underwent transplantation in first CR had an improved OS at 3 years (57% for allo-HSCT patients vs 14% for those not receiving a transplant) [19]. These data are echoed by the results of the MRC UKALLXII/ECOG2993 trial, in which 3-year OS seemed to be highly influenced by whether the patient received an allograft (59% for allo-HSCT vs 28% for those who did not). This finding led the investigators to state that the magnitude of benefit provided by imatinib in patients not receiving allo-HSCT is unclear, as the percentage of patients with long-term survival is not far from the rate achievable in the pre-imatinib era (i.e., 19% at 5 years for patients pre-imatinib with no allo-HSCT) [20•].

Outcome after transplantation also appears to be influenced by whether a patient received TKI therapy or conventional chemotherapy [52]. Patients who successfully underwent allo-HSCT in the Japan Adult Leukemia Study Group (JALSG) Ph+ ALL202 study (n=51) were compared with a group of transplant patients from the pre-imatinib era (n=122). With 3 years of follow-up, OS was improved in the group exposed to imatinib (65% vs 44%, P=0.015). DFS was also improved in the imatinib group, and pretransplant imatinib was the only factor found to influence OS and DFS on multivariable analysis.

TKI Therapy After Transplantation

The optimal strategy for introducing TKIs after allo-HSCT remains an area of active research. A report from the M. D. Anderson Cancer Center briefly described the experience in employing imatinib after allo-HSCT for CML or Ph+ ALL [53]. TKI therapy was started at approximately day 34 after transplantation. As no patients had any evidence of disease resurgence at the time the decision was made to start therapy with imatinib, this can be considered posttransplant maintenance. Significant myelotoxicity necessitated dose reduction and growth-factor support in many patients. The average daily dose administered was 100 mg, substantially lower than the dose used in the nontransplant population. Furthermore, a predictable drug interaction with tacrolimus required careful attention to serum concentrations of this drug.

The CSTIBES02 trial conducted by the PETHEMA and GETH also evaluated the use of imatinib after transplantation in a prospective manner [16]. Sixteen patients underwent allo-HSCT, and imatinib (400 mg once daily) was prospectively planned after the patients had experienced full hematologic recovery. At a median of approximately 4 months after transplantation, 9 of 16 patients were able to commence maintenance therapy with imatinib. Reasons for never starting a TKI included early mortality, severe graft-versus-host disease (GVHD), and patient preference. Patients who were able to begin imatinib therapy experienced frequent dose reductions and interruptions in therapy that were due primarily to transplant-related complications. The authors concluded

that systematic use of posttransplant imatinib was met with frequent dose reduction or drug discontinuation, and the strategy for using the TKI after transplantation requires further optimization.

The GMALL study group is conducting an ongoing, randomized, phase 3 trial comparing the role of "up-front" posttransplant TKI versus the institution of therapy only in patients with evidence of MRD [54]. Recently, this group presented an interim analysis for the first 40 patients enrolled (n=20 for each group). Patients were randomized within 6 weeks of transplantation. The dose of imatinib intended was 600 mg once daily, and the goal was to treat patients for 1 year of PCR negativity. In the up-front group, 17 of 20 patients actually started imatinib therapy. In both groups, doses typically had to be reduced to 400 mg daily. With a median follow-up of 438 days, no patient in either group who underwent transplantation in first CR has relapsed. In most patients, imatinib was discontinued prematurely because of gastrointestinal toxicity or GVHD. Tolerability of TKIs after transplantation appears to be limited. Intensive monitoring with pre-emptive institution of a TKI after any detection of MRD may be the optimal approach, which will spare patients unnecessary toxicity and generally allow them to commence therapy later. Lower doses of posttransplant TKI therapy may be explored to improve patient tolerance, but these lower doses may have the potential of inducing resistance-conferring mutations. We will have to await more mature results to conclude that a pre-emptive approach is equivalent or superior to a prophylactic one.

Conclusions

The past decade has seen major advances in the management of Ph+ ALL. Front-line therapy that includes TKIs has reduced the incidence of relapse and improved long-term survival. Imatinib, started early in the treatment course and given continuously throughout consolidation, represents the current standard of care. Second-generation TKIs such as dasatinib may further improve relevant outcomes. Allo-HSCT in first CR should be considered in all patients who are fit to undergo the procedure. The role of monitoring for the presence of MRD is becoming more precisely characterized in patients with Ph+ ALL. Continuation of TKIs after transplantation has proven challenging, primarily because of transplant-related complications. The published reports with the most extensive follow-up data indicate that further improvement in treatment is badly needed. Despite progress, a substantial number of patients with Ph+ ALL will relapse and die. Novel agents and innovative use of current therapies will be necessary to further enhance the cure rate.

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References

Papers of particular interest, published recently,
have been highlighted as:
• Of importance

1. Rowley JD. Letter: a new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature. 1973;243:290–3.
2. Wetzler M, Dodge RK, Mrozek K, et al. Prospective karyotype analysis in adult acute lymphoblastic leukemia: the Cancer and Leukemia Group B experience. Blood. 1999;93:3983–93.
3. Dombret H, Gabert J, Boiron JM, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia—results of the prospective multicenter LALA-94 trial. Blood. 2002;100:2357–66.
4. Faderl S, Kantarjian HM, Thomas DA, et al. Outcome of Philadelphia chromosome-positive adult acute lymphoblastic leukemia. Leuk Lymphoma. 2000;36:263–73.
5. Fielding AK, Rowe JM, Richards SM, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the international ALL trial MRC UKALLXII/ECOG2993. Blood. 2009;113:4489–96.
6. Yanada M, Takeuchi J, Sugiura I, et al. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group. J Clin Oncol. 2006;24:460–6.
7. Hatta Y, Mizuta S, Ohtake S, et al. Promising outcome of imatinib-combined chemotherapy followed by allogeneic hematopoietic stem cell transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia: results of the Japan Adult Leukemia Study Group (JALSG) Ph+ALL202 regimen [abstract]. Blood (ASH Annual Meeting Abstracts) 2009;114. Abstract 3090.
8. Kantarjian HM, Cortes J, La Rosee P, et al. Optimizing therapy for patients with chronic myelogenous leukemia in chronic phase. Cancer. 2010;116:1419–30.
9. Hochhaus A, O'Brien SG, Guilhot F, et al. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. Leukemia. 2009;23:1054–61.
10. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med. 2001;344:1038–42.
11. Ottmann OG, Druker BJ, Sawyers CL, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. Blood. 2002;100:1965–71.
12. Kano Y, Akutsu M, Tsunoda S, et al. In vitro cytotoxic effects of a tyrosine kinase inhibitor STI571 in combination with commonly used antileukemic agents. Blood. 2001;97:1999–2007.
13. Thomas DA, Faderl S, Cortes J, et al. Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia with hyper-CVAD and imatinib mesylate. Blood. 2004;103:4396–407.

14. Thomas DA, O'Brien SM, Faderl S, et al. Long-term outcome after hyper-CVA and imatinib (IM) for de novo or minimally treated Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-ALL) [abstract]. J Clin Oncol. 2010;28:15s. Abstract 6506.
15. Tanguy-Schmidt A, de Labarthe A, Rousselot P, et al. Long-term results of the imatinib GRAAPH-2003 study in newly-diagnosed patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia [abstract]. Blood (ASH Annual Meeting Abstracts) 2009;114. Abstract 3080.
16. Ribera J-M, Oriol A, Gonzalez M, et al. Concurrent intensive chemotherapy and imatinib before and after stem cell transplantation in newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia. Final results of the CSTIBES02 trial. Haematologica. 2010;95:87–95.
17. Bassan R, Rossi G, Pogliani EM, et al. Chemotherapy-phased imatinib pulses improve long-term outcome of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: Northern Italy Leukemia Group protocol 09/00. J Clin Oncol. 2010;28:3644–52.
18. Fang G, Kim CN, Perkins CL, et al. CGP57148B (STI-571) induces differentiation and apoptosis and sensitizes BCR-ABL-positive human leukemia cells to apoptosis due to antileukemia drugs. Blood. 2000;96:2246–53.
19. Pfeifer H, Goekbuget N, Volp C, et al. Long-term outcome of 335 patients receiving different schedules of imatinib and chemotherapy as front-line treatment for Philadelphia-positive acute lymphoblastic leukemia (Ph+ALL) [abstract]. Blood (ASH Annual Meeting Abstracts) 2010;116. Abstract 173.
20. • Fielding AK, Buck G, Lazarus HM, et al.: Imatinib significantly enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia; final results of the UKALLXII/ECOG2993 trial [abstract]. Blood (ASH Annual Meeting Abstracts) 2010, 116:Abstract 169. *This represents one of the largest studies to date of patients with Ph+ ALL. The results indicate that allogeneic stem cell transplantation still has a major role for patients managed with chemotherapy combined with imatinib.*
21. Schultz K, Bowman W, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a Children's Oncology Group study. J Clin Oncol. 2009;27:5175–81.
22. Wassmann B, Pfeifer H, Goekbuget N, et al. Alternating versus concurrent schedules of imatinib and chemotherapy for Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). Blood. 2006;108:1469–77.
23. Campana D. Minimal residual disease in acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2010;7–12.
24. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med. 2009;360:2730–41.
25. Pane F, Cimino G, Izzo B, et al. Significant reduction of the hybrid BCR/ABL transcripts after induction and consolidation therapy is a powerful predictor of treatment response in adult Philadelphia chromosome-positive acute lymphoblastic leukemia. Leukemia. 2005;19:628–35.
26. Wassmann B, Pfeifer H, Stadler M, et al. Early molecular response to post-transplantation imatinib determines outcome in MRD+ Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). Blood. 2005;106:458–63.
27. Lee S, Kim DW, Cho B, et al. Risk factors for adults with Philadelphia-chromosome positive acute lymphoblastic leukaemia in remission treated with allogeneic bone marrow transplantation: the potential of real-time quantitative reverse-transcription polymerase chain reaction. Br J Haematol. 2003;120:145–53.
28. Yanada M, Sugiura I, Takeuchi J, et al. Prospective monitoring of BCR-ABL1 transcript levels in patients with Philadelphia-chromosome positive acute lymphoblastic leukaemia undergoing imatinib-containing chemotherapy. Br J Haematol. 2008;143:503–10.
29. Ravandi F, Thomas DA, O'Brien S, et al. Dynamics of minimal residual leukemia after combinations of the hyperCVAD regimen with imatinib or dasatinib in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia [abstract]. Blood (ASH Annual Meeting Abstracts) 2010;116. Abstract 2127.
30. Holowiecki J, Krawczyk-Kulis M, Giebel S, et al. Status of minimal residual disease after induction predicts outcome in both standard and high-risk Ph- adult acute lymphoblastic leukemia. The Polish Adult Leukemia Group ALL-4-2002 MRD Study. Br J Haematol. 2008;142:227–37.
31. Ottmann O, Dombret H, Martinelli G, et al. Dasatinib induces rapid hematologic and cytogenetic responses in adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia with resistance or intolerance to imatinib: interim results of a phase II study. Blood. 2007;110:2309–15.
32. Jones D, Thomas D, Yin CC, et al. Kinase domain point mutations in Philadelphia chromosome-positive acute lymphoblastic leukemia emerge after therapy with BCR-ABL kinase inhibitors. Cancer. 2008;113:985–94.
33. Soverini S, Vitale A, Poerio A, et al. Philadelphia-positive acute lymphoblastic leukemia patients already harbor BCR-ABL kinase domain mutations at low levels at the time of diagnosis. Haematologica. 2011;96:552–7.
34. Hu Y, Liu Y, Pelletier S, et al. Requirement of SRC kinases Lyn, Hck and Fgr for BCR-ABL1-induced B-lymphoblastic leukemia but not chronic myeloid leukemia. Nat Genet. 2004;36:453–61.
35. Shah NP, Tran C, Lee FY, et al. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science. 2004;305:399–401.
36. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. N Engl J Med. 2006;354:2531–41.
37. Branford S, Melo JV, Hughes TP. Selecting optimal second-line tyrosine kinase inhibitor therapy for chronic myeloid leukemia patients after imatinib failure: does the BCR-ABL mutation status really matter? Blood. 2009;114:5426–35.
38. Lilly MB, Ottmann OG, Shah NP, et al. Dasatinib 140 mg once daily versus 70 mg twice daily in patients with Ph-positive acute lymphoblastic leukemia who failed imatinib: results from a phase III study. Am J Hematol. 2010;85:164–70.
39. Sprycel (dasatinib) Package Insert. Princeton, NJ. Bristol-Myers-Squibb Company. October 2010.
40. • Ravandi F, O'Brien S, Thomas D, et al. First report of phase II study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. Blood 2010;116:2070–7. *This is the first report with sufficient follow-up data describing the combination of a second-generation tyrosine kinase inhibitor with intensive chemotherapy for Ph+ ALL.*
41. Weisberg E, Manley PW, Breitenstein W, et al. Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. Cancer Cell. 2005;7:129–41.
42. Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. N Engl J Med. 2006;354:2542–51.
43. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010;362:2251–9.
44. Kang BW, Moon JH, Chae YS, et al. Pre-emptive treatment with nilotinib after second allogeneic transplantation in a Philadelphia chromosome-positive acute lymphoblastic leukemia patient with high risk of relapse. Acta Haematol. 2010;123:242–7.

45. Castillo E, Al-Rajabi R, Pandya DM, et al. A pilot study of the combination of nilotinib and hyper-CVAD for Philadelphia chromosome-positive acute lymphocytic leukemia and lymphoid blast crisis chronic myelogenous leukemia [abstract]. Blood (ASH Annual Meeting Abstracts) 2010;116. Abstract 2144.
46. Soverini S, Gnani A, Colarossi S, et al. Philadelphia-positive patients who already harbor imatinib-resistant Bcr-Abl kinase domain mutations have a higher likelihood of developing additional mutations associated with resistance to second- or third-line tyrosine kinase inhibitors. Blood. 2009;114:2168–71.
47. Ravandi F, Kebriaei P. Philadelphia chromosome-positive acute lymphoblastic leukemia. Hematol Oncol Clin N Am. 2009;23:1043–63.
48. O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell. 2009;16:401–12.
49. Cortes J, Talpaz M, Bixby D, et al. A phase 1 trial of oral ponatinib (AP24534) in patients with refractory chronic myeloid leukemia (CML) and other hematological malignancies: emerging safety and clinical response findings [abstract]. Blood (ASH Annual Meeting Abstracts) 2010;116. Abstract 210.
50. Dombret H, Gabert J, Boiron MJ, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia—results of the prospective multicenter LALA-94 trial. Blood. 2002;100:2357–66.
51. Thomas DA. Philadelphia chromosome-positive acute lymphoblastic leukemia: a new era of challenges. Hematology Am Soc Hematol Educ Program. 2007;435–43.
52. Mizuta S, Matsuo K, Yagasaki F, et al. Pre-transplant imatinib-based therapy improves the outcome of allogeneic hematopoietic stem cell transplantation for BCR-ABL-positive acute lymphoblastic leukemia. Leukemia. 2011;25:41–7.
53. Anderlini P, Sheth S, Hicks K, et al. Re: imatinib mesylate administration in the first 100 days after stem cell transplantation. Biol Blood Marrow Tr. 2004;10:883–4.
54. Wassmann B, Pfeifer H, Bethge W, et al. Up-front versus minimal residual disease triggered imatinib after stem cell transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia; interim results of a randomized phase III GMALL study. Bone Marrow Transpl. 2009;43 suppl 1:S48.