# Current Treatment of Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia

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**The author discusses both the standards of care and more controversial areas in the treatment of Philadelphia chromosome–positive acute lymphoblastic leukemia.**

## Introduction

Approximately one-fourth of adult acute lymphoblastic leukemia (ALL) expresses the oncogenic protein *BCR-ABL*[1] that results from the t (9;22) chromosome translocation known as the Philadelphia (Ph) chromosome. Formerly seen as a poorly tractable therapeutic problem, Ph-positive ($Ph^+$) ALL is associated with at least a 10% lower chance of complete remission (CR) than Ph-negative ($Ph^-$) disease and with an extremely poor prognosis overall, with a median survival of 8 months.[2] However, multiple clinical trials of *BCR-ABL*–specific tyrosine kinase inhibitors (TKIs) have conclusively demonstrated significantly superior initial responses resulting in higher CR rates without additional toxicity. In addition, studies are beginning to suggest that better long-term outcomes are also possible. There is little or no evidence to date that allogeneic hematopoetic stem cell transplantation (alloHCST), the toxic mainstay of treatment for this disease, is yet (or will ever be) a dispensable part of therapy. Therefore, key challenges in the treatment of $Ph^+$ ALL are the selection of appropriate pretransplantation therapy, the minimization of transplantation toxicity, the correct use of TKIs after transplantation, and the appropriate use of and response to BCR-ABL monitoring. The increasing use of reduced-intensity conditioning (RIC) as preparative regimens may mean that one or more of the key challenges will require a different response to that which is appropriate when myeloablative regimens are used, but there are few data to guide practice at present.

Because there are already several clear and cogent summaries of how to treat $Ph^+$ ALL, this review summarizes older data and noncontroversial areas of practice succinctly and focuses in more detail upon areas of practical concern for which there are emerging data or as yet no clear right answer. "Long-term" outcomes within this article refer to studies with $> 3$ years of follow-up. When the follow-up was less than this, either the time of reporting is quoted or the term "short-term" outcome is used.

## Remission induction

Table 1 shows the outcomes of numerous studies in de-novo $Ph^+$ ALL in which a TKI has been added to conventional induction therapy, given in conjunction with steroid alone, or given with less intensive chemotherapy. CR rates are, notably, always $> 90\%$. Based on these data, there is now no rationale for omitting a TKI from the initial induction treatment.

Instead, it is now logical to ask whether there is a rationale for reducing or omitting cytotoxic agents from initial induction treatment altogether. Several studies have reported, at least in abstract form, the initial outcome of giving TKIs without with only minimal chemotherapy.[3-5] Taking a closer look at the CR rates reported, most studies show that the major reason that a 100% CR rate is not reported are deaths during induction. However, where chemotherapy is minimized or excluded, studies have reported 100% CR.[3-5] The first study in which this occurred was a Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) study reported by Vignetti et al, all the more remarkable in that the study included an older population with a median age of 69. Given imatinib 800 mg/d along with prednisolone 40 mg/m$^2$ for 45 days, all patients entered remission with minimal toxicity and many did not need hospitalization. Median survival was 20 months. A further study from the GIMEMA group, LAL1205, which has been published to date only in abstract form,[3] has investigated the use of dasatinib and steroids without chemotherapy as induction in patients from the age of 18 upwards. Once again, the CR rate was 100% with no induction fatalities. These results are impressive and represent a clear and remarkable improvement in the short-term fate of patients with $Ph^+$ ALL.

However, the long-term outcome of a chemotherapy-free induction strategy is not assessable. The patients reported by Vignetti et al were not eligible for "definitive therapy," namely BM transplantation, due to their advanced age. Participants in the second study reported by Foa et al went off study after induction, obscuring the effects on long-term outcome. Two further studies, neither of which has been published to date, have reported short-term, preliminary results when TKIs were added to "minimal" chemotherapy. The French Group for Research in Adult Acute Lymphoblastic Leukemia (GRAALL) study[5] carried out a randomized comparison of imatinib combined with hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) against imatinib with dexamethasone and vincristine only during induction. Notably, 100% of patients in the "minimal" chemotherapy arm achieved CR, but only 96% in the more intensively treated arm, with toxicity being responsible for the difference. Again, the long-term consequences of a minimal chemotherapy induction strategy are as yet unclear, but this important study will eventually shed light on the issue. A further study from the European Working Group on ALL (EWALL) collaboration led by Philippe Rousselot[6] has examined a dasatinib and "minimal chemotherapy" induction regimen (namely vincristine and dexamethasone) combination in older individuals with a median age of 69. Of the 71 subjects enrolled, 90% achieved CR. Median overall survival (OS) was 27 months. Most relapses were associated with the T315I *BCR-ABL* mutation. It is not clear whether the addition of a more intensive chemotherapy regimen might have prevented that.

Despite the initial appeal of no-chemotherapy strategies, recent murine data suggest that the addition of chemotherapy to dasatinib

Table 1. Studies of TKI in de novo Ph$^+$ ALL

| Study | Study group | Drug, dose, mg | N | CR, % | Transplantation rate, % | OS |
|---|---|---|---|---|---|---|
| **Published studies** | | | | | | |
| Thomas[8] | MD Anderson | Im 400 | 20 | 93 | 50 | 75% at 20 mo |
| Yanada[29] | JALSG | Im 600 | 80 | 96 | 61 | 75% at 1 year |
| Wassmann[38] | GMALL | Im 4–600 | 92 | 95 | 77 | 36% (alternating schedule)<br>43% (concurrent schedule at 2 y |
| De Labarathe[39] | GRAALL | Im 600 | 45 | 96 | 48 | 65% at 18 mo |
| Vignetti[4] | GIMEMA | Im 800 | 30 | 100 | N/A | 74% at 12 mo |
| Ottman[27] | GMALL | Im 600 | 55 | 96 (imatinib) 50 (chemo) | N/A | 42% at 24 mo |
| Ribera[40] | PETHEMA | Im 400 | 30 | 90 | 70 | 30% at 4 y |
| Bassan[41] | NILG | Im | 59 | 92 | 63 | 38% at 5 y |
| Schultz[14] | COG | Im 340/m$^2$ | 92 | Not stated | N/A* | 80% (EFS) at 3 y |
| Ravandi[9] | MD Anderson | Das 50 bd (or 100 od) | 35 | 94 | N/A as not part of protocol | 64% at 24 mo |
| **Unpublished studies** | | | | | | |
| Fielding[11] | NCRI/ECOG | Im 600 | 145 | 95 | 44 | 43% at 3 y |
| Chalandon[5] | GRAALL | Im 800 | 188^ | 100 (imatinib DIV) 96 (imatinib hyper-CVAD) | 62 | 62% at 2 y |
| Foa[3] | GIMEMA | Das 70 bd 12 weeks | 48 | 100 | N/S | 80,7% at 10 mo |
| Rousselot[6] | EWALL | Das 140 od (100 od > 70 y) | 71 | 90 | N/A | Median 27.1 mo |

JALSG indicates Japanese Adult Leukaemia Study Group; NILG, Northern Italian Leukaemia Group; COG, Children's Oncology Group; NCRI/ECOG, UK National Cancer Research Institute/Eastern Cooperative Oncology Group; Im, imatinib; and Das, dasatinib.

treatment might help to prevent the emergence of dasatinib-resistant mutations in *BCR-ABL*.[7] Ph$^+$ ALL was generated in mice by administering *Arf*-null, *BCR-ABL*–expressing cells. The disease responded to treatment with dasatinib, but after prolonged dasatinib exposure, *BCR-ABL* kinase domain mutations were detected in mice with relapsed disease. When dexamethasone and L-asparaginase were added to the therapy, there was a more prolonged clinical response that was accompanied by the emergence of significantly fewer kinase domain mutations. There is probably an optimal intensity of chemotherapy for combination with TKIs that helps to maintain medium- to long-term responses without adding therapy-related mortality. As yet, that optimal combination is not clear, but it is a pressing and important question for future consideration.

Another very pertinent question concerns the optimal choice of TKI for induction. Dasatinib, offering simultaneous inhibition of both tyrosine and *SRC* kinases, may theoretically holds out more promise of long-term benefit than imatinib, which offers TK inhibition alone. No randomized study has yet been carried out. Some inferences regarding remission induction can be made from existing studies. When given with steroid alone, we have already seen that both agents can generate 100% CR rates. In relation to chemotherapy combinations, the MD Anderson group have studied sequentially the combination of both imatinib (n = 20)[8] and dasatinib (100 mg/d, n = 35)[9] with the hyper-CVAD regimen. Percentage CR rates were similar, 93% and 94%, respectively, but with such small numbers the comparison is barely robust. Neither study reported outcomes beyond 24 months, which approximately reaches the median survival times generally reported for TKI-containing regimens. At the time of reporting of the dasatinib combination, the median survival was not yet reached. However, with 75% disease-free survival (DFS) at 20 months for imatinib and a projected 64% DFS at 24 months for dasatinib, there is no immediate short- to medium-term survival difference apparent. However, the dasatinib combination regimen generated 16 episodes of bleeding and 8 episodes of pleural effusion, whereas the specific toxicity of imatinib was minimal. Results of studies to date cannot explicitly justify adding dasatinib to chemotherapy combinations for the therapy of de-novo Ph$^+$ ALL.

## Postremission therapy and allogeneic stem cell transplantation

Although many studies show early benefits to TKI treatment, evidence of a survival benefit has only recently emerged, because many of the initial studies reported early. However, a recent Italian study[10] of 94 patients treated with imatinib and chemotherapy included a nonrandomized, historical control group receiving the same chemotherapy treatment but without imatinib. The patients who received imatinib in their regimen had a 5-year OS of 38% compared with 23% in the control group. A second study including a control group receiving the same chemotherapy without imatinib has been carried out by the UK National Cancer Research Institute (NCRI)/US Eastern Cooperative Oncology Group (ECOG) collaboration and has recently been reported in abstract form.[11] There was a large, apparently imatinib-attributable difference in outcome: OS was 23% in the pre-imatinib cohort compared with 43% when imatinib was added. However, careful analysis revealed a considerably higher rate of alloHSCT in the imatinib cohort. On examination of the comparative outcomes of those not receiving imatinib, the addition of imatinib to chemotherapy in the absence of myeloablative alloHSCT did not result in a significant survival benefit, even when patients who did not survive in remission to the median time to alloHSCT were excluded. Therefore, at least after imatinib-containing induction regimens, myeloablative alloHSCT does not appear to be dispensable if the optimal long-term outcome is to be achieved. Where imatinib-based induction and myeloablative alloHSCT are combined, excellent 3-year OS rates are to be expected despite the risk of myeloablative alloHSCT. The relevant 3-year OS in UKALL12/E2993 was 59%. An abstract report on successive German Multi Centre ALL (GMALL) studies in Ph$^+$ ALL[12] also

Table 2. Studies of RIC alloHSCT regimens in patients with ALL

| Study | Center/ registry/ multicenter | Median age (total population) | $Ph^+$, N | $Ph^+$ CR1, N | Conditioning regimen | TKI after alloHSCT? | TRM, % (total population) | CGVHD, % (total population) | OS $Ph^+$ subgroup |
|---|---|---|---|---|---|---|---|---|---|
| Arnold[42] | M | 38 | 11 | 3 | Flu/Bu ± ATG | No | 45 | 46 | N/S |
| Martino[43] | M | 50 | 11 | 3 | Various | N/S | 23 | 72 | N/S |
| Mohty[44] | R | 38 | 37 | N/S | Various | N/S | 28 | 37 | N/S |
| Stein[41] | S | 47.5 | 9 | 6 | Flu/Mel | Various | 21.5 | 86 | N/A |
| Bachanova[45] | S | 49 | 14 | 10 | Flu/Cy/TBI 2 Gy | Only for morphological or to relapse | 27 | 45 | N/A |
| Ram[24] | S | 57 | 25 | 19 | Flu/TBI 2 Gy | 4–600 mg daily, upon count recovery, for 1 year | 28 | 44 | 62% 3 y |

N/A indicates numbers too small/status at transplantation too various to give a single figure; N/S, not specified; TBI, total body irradiation; Flu, fludarabine; Bu, bulsuphan; Mel, melphalan; Cy, cyclophosphamide; ATG, anti-thymocyte globulin; S, single; R, registry; and M, multicenter.



revealed that excellent outcomes can be achieved with myeloablative alloHSCT when an imatinib-based induction is used; OS at 3 years was 72%. A recent Japanese Adult Leukaemia Study Group also reports a 3-year OS probability of 65% after imatinib-based induction and myeloablative alloHSCT.[13] Both the UK/ECOG and GMALL studies reported a poor outcome when transplantation was not achieved despite the inclusion of imatinib in the protocols.

A caveat to the nondispensability of alloHSCT has been raised by the Children's Oncology Group (COG),[14] which carried out a study in which patients up to the age of 21 were treated with imatinib added to chemotherapy in cohorts, with the final cohort receiving continuous imatinib. The protocol did not allow for matched unrelated donor (MUD) alloHSCT. This decision, which differs from recommendations given in all studies of adult $Ph^+$ ALL, was based on an international study in children[15] showing a 43% treatment-related mortality (TRM) for MUD alloHSCT. Despite the low relapse rate after MUD allo-HSCT, this unacceptably high TRM negated a survival advantage when outcomes were compared with those in children receiving chemotherapy alone. This policy left a small cohort of children who received an imatinib/chemotherapy combination without alloHSCT. There was a relatively high rate of off-protocol MUD alloHSCT that makes data interpretation more difficult. However, at 3 years, the outcomes for those treated with imatinib/chemotherapy ($n = 25$) compared favorably to those treated with alloHSCT ($n = 21$), with an 85% 3-year DFS without alloHSCT. Although the study was neither designed nor powered to answer the question of whether imatinib/chemotherapy could replace sibling alloHSCT for children with $Ph^+$ ALL, the data have introduced the hypothesis that children with $Ph^+$ ALL can be treated successfully without alloHSCT. It will be very important to look at the long-term follow-up of that study.

## Nonmyeloablative (RIC) alloHSCT

Myeloablative alloHSCT carries considerable risk of TRM and is not applicable to older individuals. Opinions vary on the upper age limit for the procedure; in UKALL12/E2993, a very high TRM of nearly 40% was observed in patients older than 35 years of age receiving myeloablative allo-HSCT, resulting in a protocol limit of 40 years of age in the current UK NCRI study, UKALL14. In some studies, patients are offered myeloablative alloHSCT up to the age of 55 years. Not surprisingly, RIC is beginning to gain more widespread use. Although prospective studies of this approach are ongoing, none has been reported to date, which means that published, retrospective reports must be interpreted with caution due to the problems of selection bias and immortal time bias. To confound interpretation of the data further, most published series include patients beyond CR1 and none is confined to $Ph^+$ ALL. Nonetheless, a realistic overview of what can be achieved using this approach in high-risk ALL is beginning to emerge. A summary of reports of RIC approaches to the treatment of $Ph^+$ ALL is given in Table 2. The numbers of patients treated in CR1 only are recorded in the table because the clearest theme running through all of the studies to date is that if patients with relapsed or resistant disease or beyond CR1 undergo transplantation, the outcomes are dismal and the mortality very high.

However, when considering this approach as used in CR1, a few key, positive messages emerge. First, RIC regimens can be used with an acceptable TRM in patients who are typically older than those suitable for a myeloablative approach. Median ages reported range from 38 to 50 years, and TRM in more recent studies, which include more patients in CR1, is consistently between 20% and 30%. No particular conditioning regimen can be deduced to be optimal yet. cGVHD rates are high, and there is insufficient evidence to determine whether the high rate of GVHD is positively associated with a better disease-related outcome. There are likely to be trials using approaches in which conditioning regimens that have a lower risk of cGVHD are investigated. In summary, nonmyeloablative alloHSCT approaches appear promising, offering DFS rates in $Ph^+$ ALL, which, where overtly specified, appear to be higher than could be obtained with chemotherapy and imatinib alone and are in line with what has been achieved using myeloablative approaches. A comparative study of European Group for Blood and Marrow Transplantation (EBMT) registry reports of the outcome of myeloablative versus RIC alloHSCT in patients with ALL confirms this impression.[16] Indeed, in a multivariate analysis, the type of conditioning regimen was not significantly associated with leukemia-free survival. RIC approaches should be vigorously pursued as part of prospective studies in order to define their role in ALL. In $Ph^+$ ALL in particular, inquiry into the role of TKIs after alloHSCT is vital. The forthcoming study from the UK NCRI, UKALL14, will assign all patients with ALL 40 years of age or more than to a nonmyeloablative approach with fludarabine, melphalan, and alemtuzumab in an attempt to obtain good disease control with less GVHD.

## What treatment should be offered to patients with poor donor options?

Despite initial responses, long-term outcomes, at least in adults, remain unsatisfactory when TKI/chemotherapy combinations are used without alloHSCT. Does this justify the use of alternative, higher-risk donor and conditioning options in relation to 1 or

2 antigen mismatch unrelated donor (MMUD), haploidentical and umbilical cord blood (UCB) transplantations? It is hard to be sure exactly how the higher risk of TRM balances against the increased risk of relapse. Haploidentical alloHSCT often results in a very high TRM. A series including 60 cases of ALL has been reported, of which, only 15 cases were $Ph^+$ and approximately half were beyond CR1. These data have been recently reviewed in detail.[17] UCB HSCT in adults has a higher TRM than MUD HSCT. However, where the donor is not fully matched, UCB is arguably a better option.[18] A recent report from Japan[19] documented 8 adults with $Ph^+$ ALL who, after a median of 26 months of follow-up, had an estimated 3-year OS of 100% and a leukemia-free survival of 85%. However, this is a small number of patients and such good results with minimal toxicity are not typical of cord blood transplantations in adults. As counterbalance, a recent report from the University College London (UCL) group of 50 patients receiving MMUD grafts after RIC for a variety of disorders, including acute leukemias, there was no difference in 3-year OS (53% vs 49%, $P = .44$) between fully matched and MMUD even though the mismatch occurred at the antigenic level in 40 cases.[20]

Balanced against the toxicity of high-risk transplantation approaches is the high risk of relapse without a alloHSCT and the lack of clear guidance in the literature as to how best to combine TKIs with consolidation and maintenance therapy or whether to continue with TKI treatment after the typical maintenance period of 2 years. Given the difficulty in balancing these approaches for patients with poor donor options, these situations must currently be tackled on a case-by-case basis, taking into careful account the preferences and expectations of the patient.

## Autologous transplantation

Autologous transplantation remains a possible therapeutic option in ALL. Although the large randomized controlled trial UKALL12/EOCG2993[21] demonstrated inferiority compared with continued chemotherapy, there may be circumstances when clinicians consider this to be a reasonable option. There are anecdotal reports of good outcomes when autologous transplantation is used when minimal residual disease is not present before the procedure. There are no data on how best to use TKIs after autologous transplantation for $Ph^+$ ALL.

## The role of TKIs after alloHSCT

A very important and as yet unanswered question concerns whether TKIs should be administered after alloHSCT and under what circumstances. Programa para el Estudio de la Terapéutica en Hemopatía Maligna (PETHEMA) study reported that imatinib was poorly tolerated after myeloablative alloHSCT; only 62% of patients were able to start at median of 3.9 months after alloHSCT, and many patients required discontinuation or dose reduction. An ongoing GMALL study for which preliminary results have only been reported in abstract form[22] randomized patients after HSCT to either "up-front" imatinib beginning at 3 months after alloHSCT wherever possible or imatinib started only upon any *BCR-ABL* reappearance. This study also reported poor tolerance of imatinib when given early after alloHSCT. In contrast, most patients who started imatinib after the detection of *BCR-ABL* had a prompt suppression of *BCR-ABL* in response to the drug, and to date there is no difference in outcome between the groups. A small, nonrandomized, single-center study from the University of Minnesota[23] showed a trend toward improved outcome in patients who could be treated with imatinib in the pre- and posttransplantation period after cyclophosphamide and TBI myeloablative conditioning. Similarly, Ram et al[24] reported that imatinib given for a median duration of 11.5 months after RIC with fludarabine and 2 Gy of TBI (which was relatively well tolerated after transplantation, with only 3 of 18 patients needing to stop the drug) was associated with significantly reduced mortality on univariate analysis, although the effect on relapse was not statistically significant. There is insufficient evidence to conclude that imatinib should be given to all patients after alloHSCT. However, outside of a clinical trial, careful consideration should be given on a patient-by-patient basis as to whether and when to start imatinib. Regular and quantitative *BCR-ABL* monitoring in an accredited laboratory is strictly necessary if an expectant policy is to be followed. The next section provides additional information about *BCR-ABL* monitoring in $Ph^+$ ALL.

## Role of *BCR-ABL* monitoring in $Ph^+$ ALL

Real-time PCR *BCR-ABL* quantification is often used to monitor minimal residual disease in patients with $Ph^+$ ALL, but optimal practice and interpretation of results is unclear. In addition, while there is considerable standardization of methodology for p210 quantification, there is less standardization for p190 quantification. Within the European Union, the European Study Group's (ESG) twice annual quality control rounds are helping to define a pan-European standard, but at the time of writing there is still variation in practice and reporting among participating laboratories. In addition, there are conflicting reports on the association between an initial decrease in *BCR-ABL* transcript level and long-term outcome. In the "pre-imatinib" era, good correlation between *BCR-ABL* transcript levels and outcome has been reported.[25,26] After clinical trials including TKIs, *BCR-ABL* transcript levels have also been correlated with response.[27] Unlike in chronic myeloid leukemia, there is no consensus on what represents an optimal response. However, Lee et al[28] were able to demonstrate that a 3-log reduction in *BCR-ABL* transcripts after 1 month of imatinib treatment strongly predicted a reduced relapse risk.[28] In contrast, Yanada et al[29] observed no association between rapid achievement of *BCR-ABL* negativity and long-term outcome after an initial imatinib/chemotherapy induction regimen.[29] The long-term outcome in relation to *BCR-ABL* response to induction is hard to predict. There are now 2 reports that low-level subclones harbor point mutations in the *BCR-ABL* kinase domain at diagnosis.[30,31] Both studies demonstrated that the presence of mutated *BCR-ABL* clones at diagnosis did not preclude an initial "good" *BCR-ABL* response. Pragmatically, imatinib- and dasatinib-containing regimens can be expected to generate complete clinical response in 95%-100% of patients. Eligible patients will be treated with alloHSCT wherever possible, and for these patients, *BCR-ABL* monitoring early in the course of the disease is unlikely to change practice at present. For patients not receiving alloHSCT, serial monitoring during initial therapy is of more relevance because it might prompt a switch of therapy before hematological relapse.

In the future, when there is more understanding of the kinetics of *BCR-ABL* mutations, a wider range of TKIs available, and a greater understanding of the relationship between different *BCR-ABL* subclones and long-term outcomes, the practice of *BCR-ABL* and serial mutation monitoring is likely to change and to assume greater importance. However, currently, the most immediate impact of *BCR-ABL* monitoring is on therapy after alloHSCT, when various manipulations such as immunosuppression reduction, addition of TKIs, and the use of donor lymphocyte infusions are readily available. However, there are few data to guide strategy. The

Table 3. Ongoing studies of novel agents in Ph$^+$ ALL

| Title | Inclusion criteria | Sponsor | Clinical trial.gov identifier |
|---|---|---|---|
| A Phase 1/2 Study of SNDX-275 in Combination With Imatinib for Relapsed/Refractory Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia | Primary refractory or relapsed disease | Sidney Kimmel Comprehensive Cancer Center, USA | NCT01383447 |
| A Phase 1/2 Study Of SKI-606 (Bosutinib) In Philadelphia Chromosome Positive Leukemias | Ph$^+$ CML or Ph$^+$ ALL who are primarily refractory to full-dose imatinib (600 mg), have disease progression/relapse while on full-dose imatinib, or are intolerant of any dose of imatinib | Pfizer | NCT00261846 |
| A Phase I Dose Escalation of MK0457 in Combination With Dasatinib in Patients With Chronic Myelogenous Leukemia and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia | Patients must have CML or Ph$^+$ ALL; patients must be at least 3 mo from the start of dasatinib therapy and currently receiving dasatinib therapy for CML or Ph$^+$ ALL and evaluable for hematologic response prior to entering the study | Merck | NCT00500006 |
| To determine the dose of dasatinib that can be safely administered with cytarabine, and high-dose mitoxantrone in patients with Ph+ ALL/lymphoid blast crisis of known chronic myelogenous leukemia | Previously untreated and treated adult patients (≥18 y of age) with a diagnosis of Ph$^+$ ALL | Memorial Sloan-Kettering Cancer Center, USA | NCT00940524 |
| Nilotinib With Chemotherapy for the Treatment of Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (ALLPhi) | Newly diagnosed ALL or acute mixed lineage leukemia; positive for Bcr-Abl fusion transcript (Ph$^+$ disease) by RT-PCR | Asan Medical Center, Korea | NCT00844298 |

optimal frequency of monitoring is not clear. The relationship between *BCR-ABL* reappearance and relapse been recently questioned in a report of 2 cases of very long-term (> 10 years) remissions in the presence of persistent low-level p190 *BCR-ABL* in 2 patients with Ph$^+$ ALL after treatment with autologous HSCT without any subsequent further antileukemic therapy.[32] However, at present, the balance of evidence suggests that *BCR-ABL* should be monitored after alloHSCT and that reemergence of *BCR-ABL* is a rational basis for intervention.

## Resistance to TKIs and novel agents for use in this scenario

The emergence of *BCR-ABL* mutations that confer resistance to one or more TKIs is likely to confirm the clinical observations from large trials showing that, without transplantation, long-term DFS survival is not optimal. Mutations are most frequent within the kinase domain of *BCR-ABL* and can occur within the A (activation) loop, the P (ATP-binding) loop, or at the so-called "gatekeeper" residue, threonine 315. We have already noted in this review that more than 1/3 of patients present with small subpopulations containing *BCR-ABL* mutations. Mutations can also be acquired or emerge under the selection pressure of TKI treatment.[33] The emergence of mutations is associated with hematological relapse, as demonstrated in the EWALL study in older patients, in whom serial monitoring for the T315I mutation showed that a rise of > 0.1% was always associated with relapse.[6] However, the interval between rise of T315I signal and clinical relapse was 1-3 months in half of the patients and concomitant in the other half, giving little leeway for intervention in many. Novel agents active in the setting of the T315I and other mutations are under clinical study. Ponatinib (AP24534) is a potent pan-*BCR-ABL* inhibitor with activity against all tested imatinib-resistant mutants, including T315. In a recent phase 1 study,[34] most patients had chronic myeloid leukemia, but 3 had Ph$^+$ ALL. Elevation of pancreatic enzymes and pancreatitis were dose-limiting toxicities. A dose of 45 mg orally was chosen for further study. At this dose, responses were observed in patients with the T315I mutation whose disease was resistant to dasatinib.

Blinatumomab, a bispecific, T-cell-engaging antibody binding CD19 and Cd3, is a novel agent with potential for efficacy in patients at high risk of disease relapse. In a small study of patients with a persistent or new appearance of molecularly determined ALL, an 80% response rate was observed (n = 21).[35] Relapse-free survival at a median follow-up of 405 days was reported without the need for additional chemotherapy. Of particular interest, activity was also demonstrable in Ph$^+$ patients with a detectable T315I tyrosine kinase domain. Overall, therapy was well tolerated, and patients who received alloHSCT (n = 8) all remain alive and in remission after transplantation (median follow-up of 434 days). Based on these preliminary data, blinatumomab is being studied in a European pivotal phase 2 study (with US centers participating) in minimal residual disease–positive adult ALL. Table 3 summarizes several ongoing trials of TKIs and other novel agents in Ph$^+$ ALL. A more exhaustive account of all trials in Ph$^+$ ALL can be found at www.clinicaltrials.gov.

It follows that *BCR-ABL* mutation screening is likely to be the most clinically relevant in patients who are receiving TKIs without or without chemotherapy but without the possibility of a "definitive" alloHSCT procedure. An increase in *BCR-ABL* level or a frank hematological relapse is an important trigger for mutational analysis to select an available TKI to which the patient's disease might still be sensitive or to seek a clinical trial of a novel agent.

### *Relapsed Ph$^+$ ALL*

Relapsed ALL is a notoriously difficult clinical problem, and outcomes are typically extremely poor.[36] CR2 is possible in only ~ 50% of chemotherapy-treated patients. Many younger patients with Ph$^+$ ALL will have already received alloHSCT, making salvage harder and with more toxicity, particularly if chemotherapy reinduction is under consideration. However, a phase 2 study of dasatinib 140 mg/d in patients who relapsed after imatinib-containing regimens demonstrated that approximately half of the patients could achieve a CR2 with modest toxicity. However, median remission duration was only 3.3 months. Under these circumstances, a second allo-HSCT might be considered. A case report[37] shows a positive outcome for a patient who received dasatinib followed by a RIC alloHSCT after imatinib and myeloablative alloHSCT failed to control the disease. All reports of alloHSCT show a very much less than ideal outcome in patients beyond CR1. However, many of these were reported before the advent of TKIs, which might, in selected circumstances, allow for second definitive transplantation procedures.

## Disclosures

Conflict-of-interest disclosure: The author declares no competing financial interests. Off-label drug use: None disclosed.

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