Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2011 April ; 11(2): 198–203. doi:10.1016/j.clml.2011.03.002.

Managing Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Role of Tyrosine Kinase Inhibitors

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Abstract

Before the introduction of tyrosine kinase inhibitors, the prognosis for patients with Philadelphia chromosome–positive acute lymphoblastic leukemia was poor. The treatment of choice, stem cell transplantation, is a potentially curative option, but it is available only for a minority of patients and is associated with significant risk of morbidity and mortality. Although imatinib is largely effective, a substantial proportion of patients become resistant or intolerant to it. The activity of imatinib may be enhanced by coadministration with chemotherapy; such treatment is effective in many patients. Dasatinib is established as a second-line treatment in patients with resistance to or intolerance of imatinib. Recent data suggest that dasatinib, either alone or in combination with chemotherapy, has utility as first-line therapy. Dasatinib is more potent than imatinib, is less susceptible to drug-resistance mechanisms, and has been shown to penetrate the blood-brain barrier, making it potentially effective for treating central nervous system disease. Patients who relapse during treatment with dasatinib frequently carry the T315I mutation of BCR-ABL. Future regimens combining dasatinib with an agent able to inhibit this mutation may further improve outcome.

Keywords

acute lymphoblastic leukemia; acute lymphocytic leukemia; allogeneic stem cell transplantation; dasatinib; imatinib; Philadelphia chromosome-positive

Introduction

Acute lymphocytic/lymphoblastic leukemia (ALL) is a heterogeneous group of hematologic malignancies resulting from monoclonal proliferation and expansion of lymphoid precursors in the bone marrow, blood, and other organs.¹ The Philadelphia (Ph) chromosome is the most frequent cytogenetic abnormality found in adults who have ALL (15% to 30% of patients).^{1,2} Incidence increases with age. Among patients aged 50 years or older who have ALL, more than 50% are Ph-positive (Ph+).² Ph+ ALL has an aggressive clinical course; patients have a significant risk of developing central nervous system (CNS) leukemia.³⁻⁵

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Disclosure

Dr Ravandi received research funding and honoraria from Bristol-Myers Squibb and honoraria from Novartis.

Additionally, a significant proportion of patients who have Ph+ ALL are older, with an associated poorer prognosis.⁶ Therefore, the need for effective and well-tolerated treatments for Ph+ ALL is critical.⁷

Historic Regimens

Patients who have Ph+ ALL treated solely with chemotherapy face poor outcomes. In early clinical trials, complete response rates were 46% to 96%; however, median overall survival (OS) times were typically less than or equal to 11 months.⁸ Allogeneic stem cell transplantation (alloSCT), in contrast, is potentially curative and remains the treatment of choice for adults with Ph+ ALL—all of whom are considered at high risk of relapse.⁹ However, most patients cannot find a suitable, related, histocompatible donor for alloSCT; advanced age also raises the potential for treatment-related mortality to unacceptable levels. Furthermore, available data indicate that disease status at the time of hematopoietic cell transplantation is an important predictor of outcome.¹⁰

The efficacy and practicality of alloSCT was assessed by a large, multicenter, clinical trial. The UKALL XII/Eastern Cooperative Oncology Group E2993 study evaluated the efficacy of alloSCT following complete hematologic response (CHR) achieved by standard induction therapy.¹¹ Of 267 patients who had Ph+ ALL, 82% achieved CHR. Five-year OS, event-free survival, and relapse-free survival (RFS) rates in patients who underwent SCT were significantly superior ($P = .0002$) to those for chemotherapy alone. However, if the data are adjusted for age and white blood cell count at diagnosis and if the patients who relapse before the median time to transplant are excluded, then only the RFS in the alloSCT arm remains significantly superior to chemotherapy alone. Moreover, only 28% of study patients actually underwent alloSCT. The major reasons for not proceeding with alloSCT were age older than 55 years and occurrence of pre-alloSCT events.

To enable more patients to receive dose intensification, autologous SCT has been investigated as a potentially viable transplantation technique. However, it has been shown to be inferior to alloSCT as well as to continued chemotherapy in terms of OS and disease-free survival at 3 years.¹² Alternative donor transplantations have been studied but, to date, have met with limited success.¹³

Although the role of SCT has not been supplanted in the treatment of Ph+ ALL, evidence indicates that, in the future, tyrosine kinase inhibitors (TKIs), together with conventional induction and consolidation therapy, may constitute effective treatment, widen the pool of patients eligible for SCT, and even obviate the need of initial treatment with SCT in some patients.

Imatinib in the Treatment of Ph+ ALL

Imatinib, a TKI that targets BCR-ABL, the constitutively activated tyrosine kinase product of the Ph chromosome, is now an integral component of therapy for patients who have Ph+ ALL. In an initial study, single-agent imatinib in patients with relapsed/refractory Ph+ ALL yielded limited and short-lived, yet encouraging, responses.¹⁴ These data led to a number of studies of imatinib as first-line treatment in elderly patients, who typically cannot tolerate

SCT. In a study of single-agent imatinib (plus steroids), all 30 patients achieved CHR; median survival from diagnosis was 20 months.¹⁵

The current consensus is that imatinib, administered in combination with chemotherapy, improves patient outcomes compared with chemotherapy alone (Table 1).¹⁶⁻²³ The number of patients able to receive SCT, and/or the outcomes of SCT, have improved as well.^{19,20,24,25}

Nevertheless, several limitations relating to the use of imatinib in the treatment of Ph+ leukemias have emerged. First, imatinib has a restricted ability to penetrate the blood-brain barrier—perhaps because it is a substrate of P-glycoprotein, an efflux protein of the blood-brain barrier—it is therefore ineffective at preventing or treating CNS disease.^{2,4,7,26,27}

Leis et al reported on data from a small number of patients.²⁸ Of these patients, 21% who had received imatinib and had either blast phase chronic myeloid leukemia (CML), CML with biphenotypic markers, or Ph+ ALL experienced a relapse of CNS disease. This study and two case reports^{26,29} suggest that poor penetration of imatinib (1%) into the cerebrospinal fluid may be associated with an increased risk of CNS relapse in the absence of additional prophylaxis.⁴

Second, clinical resistance to imatinib may shorten the duration of the responses and lead to eventual relapse. “Primary” imatinib resistance, which is characterized by failure to achieve CHR, is distinguished from “secondary” resistance, which develops in patients who initially respond to imatinib but then relapse despite continued treatment. In the phase 3 study of imatinib in patients who had CML,³⁰ 24% of patients did not achieve complete cytogenetic response (CCyR) at 18 months—now considered a criterion of optimum response.³¹

Multiple mechanisms have been implicated in imatinib resistance; the acquisition of point mutations within the BCR-ABL kinase domain appears to play a leading role.^{2,32,33} Imatinib may be prevented from binding by mutations at the contact site (eg, T315I) that directly hinder contact between imatinib and BCR-ABL or by mutations at the adenosine triphosphate-binding (P) or -activating (A) loops that hinder binding indirectly by altering the spatial conformation of the molecule.³⁴ Many amino acid substitutions within BCR-ABL have been identified, spanning a range of imatinib sensitivities, but the most frequently detected mutations in Ph+ ALL are T315I and certain mutations occurring in the P-loop with high insensitivity to imatinib (eg, those at Y253 and E255).^{33,35} The T315I mutation, commonly known as the gatekeeper mutation, leads to extreme insensitivity to all clinically available TKIs.³⁴ Its presence in Ph+ ALL is associated with shorter OS.³⁶ BCR-ABL mutants are present chiefly in patients presenting with relapsed disease. However, mutations (especially in the P-loop) have also been reported to exist before the initiation of imatinib treatment in approximately 40% of patients, and may subsequently be responsible for relapse during therapy.^{37,38} Other investigators have not been able to identify these mutations before treatment.³⁹

Other mechanisms of imatinib resistance include amplification of the BCR-ABL gene, decreased drug influx, and involvement of secondary downstream pathways, such as Src family kinases (SFKs), which play a major role in ALL signaling.^{2,40,41} The inability of

imatinib to inhibit SFK-dependent pathways is, therefore, a potential cause of resistance to this compound in patients who have ALL. For this reason, imatinib plus chemotherapy has not supplanted alloSCT as treatment of choice in this disease, particularly the younger patients.⁹

Patients treated with imatinib should be monitored for early signs of treatment failure, and an alternative therapy should be provided as appropriate.⁴² In addition to hematologic and cytogenetic monitoring, monitoring minimal residual leukemia by flow cytometry and/or quantitative real-time polymerase chain reaction techniques may be of value in detecting impending imatinib failure. After chemotherapy or SCT, the detection of residual BCR-ABL transcripts is associated with a high risk of subsequent relapse, and the detection of minimal residual disease (MRD) may allow for targeted therapy that could prevent a potential relapse.⁴³

The development of second-generation BCR-ABL–targeted TKIs has presented new therapeutic options for patients who become resistant to, or intolerant of, imatinib, and who are unable to benefit from SCT.

Dasatinib — Rationale for First-Line Treatment

Dasatinib is a thiazole carboxamide with potent activity against BCR-ABL and SFKs.⁴⁴ Dasatinib is active and well-tolerated in patients with imatinib resistance or intolerance across all phases of CML and Ph+ ALL.^{45–48} Dasatinib is believed to counter several mechanisms of imatinib resistance. First, commonly occurring mutations that show a high degree of insensitivity to imatinib are sensitive to dasatinib, with the exception of T315I.³⁴ Second, dasatinib has an approximately 325-fold greater in vitro activity than imatinib against native BCR-ABL^{34,44}; therefore, it is expected to overcome resistance resulting from BCR-ABL amplification. Third, unlike imatinib, dasatinib is not a substrate for organic cation transporter-1, an influx protein, and is, therefore, unlikely to be affected by decreases in its activity.⁴⁹ Finally, the activity of dasatinib against SFKs is likely to counteract imatinib resistance involving the activation of downstream pathways.⁴¹ It should also be noted that dasatinib has been reported to cross the blood-brain barrier with potential activity in CNS disease.⁵⁰

Dasatinib is approved for the treatment of patients with CML (any phase) or Ph+ ALL who are resistant or intolerant to first-line treatment, including imatinib.⁵¹ The confirmed activity and tolerability of dasatinib in the second-line treatment of Ph+ ALL, as well as its preclinical advantages over imatinib, provides rationale for first-line usage.

Proof of concept for the use of dasatinib as second-line treatment of Ph+ ALL was given in a phase 1 dose-increase study, which also included patients with any phase of CML.⁵² Encouraging drug activity was observed in 10 patients with Ph+ ALL or lymphoid blast crisis CML, with a CHR rate of 70% and a major cytogenetic response (MCyR) rate of 80%.

As a result of data from a pivotal, open-label, single-arm, phase 2 study, the US Food and Drug Administration (FDA) approved dasatinib for the second-line treatment of Ph+ ALL.^{48,53} Of the patients recruited into the study, 96% were imatinib resistant, and BCR-

ABL mutations were present in 78%; 20% of these mutations were T315I. Thirty-seven percent of patients had undergone SCT. This study showed that dasatinib 70 mg twice daily induced high response rates (Table 2),⁵³ including CCyRs in more than half of the study population. Moreover, MCyRs were achieved rapidly (median time to response, 29 days) and were relatively durable (median, 6.3 months).

The study also showed that rates of both MCyR (55% versus 56%) and CCyR (52% versus 56%) were similar in patients with or without baseline mutations; however, results were more favorable if T315I-bearing patients were excluded from the analysis; rates for MCyR and CCyR were 68% and 66%, respectively, and median progression-free survival (PFS) was 5.7 months.⁵³ MCyR rates (76% versus 45%) and median PFS (7.2 months versus 2.7 months) were also more favorable in patients who had undergone previous SCT compared with those who had not. Dasatinib was relatively well tolerated. Although grade 3-4 thrombocytopenia and neutropenia were each observed in 78% of patients,⁵³ baseline values for these events in this study were 50% and 19%, respectively.⁴⁶ The most common grade 3-4 nonhematologic toxicities were gastrointestinal bleeding (11%), diarrhea (9%), asthenia (7%), and pleural effusion (7%).⁵³

The FDA originally approved dasatinib at a dose of 70 mg twice daily for patients with Ph+ ALL and resistance to or intolerance of initial treatment, including imatinib. The activity of twice-daily dasatinib in this indication has recently been confirmed in a Japanese phase 2/3 study.⁵⁴ However, as a result of a randomized, open-label, phase 3, dose-optimization study, the FDA recently changed the approved dosage for this indication to 140 mg once daily.⁵⁵

This study evaluated whether the benefit-to-toxicity ratio in patients who have advanced CML or Ph+ ALL may be improved by altering the dosing regimen. Patients were randomized to receive either dasatinib 140 mg once daily or 70 mg twice daily. Investigators recently reported 2-year data for patients with Ph+ ALL.⁵⁵ At last follow-up, major hematologic response (38% versus 32%), MCyR, and CCyR rates were nominally greater in the 140 mg dasatinib once-daily arm, but differences between median PFS ($P = .735$) or OS ($P = .336$) values were not significant (Table 2). All major hematologic responses were achieved within 4 months.

Although both cohorts showed similar efficacy, the 140 mg once-daily arm exhibited an improved safety profile compared with the 70 mg twice-daily arm.⁵⁵ Rates of grade 3-4 thrombocytopenia (72% versus 60%) and neutropenia (67% versus 72%) were similar across the study; however, fewer patients in the once-daily arm suffered pleural effusions (all grades 18% versus 32%) or required dose reductions for toxicity (10% versus 23%).

Investigators at the MD Anderson Cancer Center have reported preliminary results of a study of dasatinib combined with chemotherapy (hyperCVAD) as treatment for relapsed Ph + ALL (n = 14) or lymphoid blast phase CML (n = 9).⁵⁶ Patients received dasatinib 50 mg twice daily for the first 14 days of eight cycles of chemotherapy (alternating blocks of high-dose hyperCVAD and high-dose cytarabine plus methotrexate) as induction therapy. Patients achieving CHR then received dasatinib plus vincristine and prednisone monthly for 2 years, followed by dasatinib alone indefinitely. Data from patients assessed to date show

this combination to be feasible and effective (Table 2). Although caution must be used in interpreting the data from this small group of patients, results suggest that activity with this regimen may be greater than that with dasatinib alone in this indication. After a median response duration of 26 weeks, 9 patients relapsed, 5 of whom acquired T315I or F317L mutations. Grade 3 toxicity has primarily involved bleeding or pleural effusion. At the time of reporting, 7 patients have died after relapse, 1 after SCT, 4 from infection, and 1 from unknown causes.

Dasatinib as First-line Therapy

In 2008, investigators reported final results for patients enrolled in the Gruppo Italiano Malattie Ematologiche Ddell'Adulto LAL 1205 study. This open-label, single-arm study demonstrated that, in adults with de novo Ph+ ALL, dasatinib monotherapy was able to induce CHR in all evaluable patients, irrespective of age, with limited toxicities and no fatalities (Table 3).⁵⁵⁻⁵⁷ Patients received dasatinib 70 mg twice daily for 12 weeks, following a steroid pre-phase. After a median follow-up of 11.2 months, the 10-month OS rate was 81%. At last report, relapses had been recorded in 9 (19%) patients. Mutational analysis was performed in 8 of these patients; 5 carried the T315I mutation, and 1 patient displayed E255K. No fatalities had been observed.

Dasatinib plus chemotherapy (hyperCVAD) is also being examined as first-line treatment for patients with Ph+ ALL.⁵⁸ In this open-label, single-arm, phase 2 study, 35 treatment-naïve patients received the MD Anderson treatment schedule described above. Dasatinib 100 mg once daily or 50 mg twice daily were administered during the first 14 days of each course of chemotherapy. High activity was recorded; more than 75% of patients achieved major molecular responses (Table 3). Grade 3 toxicity has primarily included gastrointestinal bleeding, myelosuppression, and pleural effusions.

Dasatinib in combination with chemotherapy is also being studied as first-line treatment in patients who are older than 55 years who have untreated Ph+ ALL.⁵⁹ In this study, treatment consists of a steroid pre-phase followed by induction therapy with dasatinib 100 mg to 140 mg once daily in combination with four weekly cycles of vincristine and dexamethasone. Consolidation treatment comprises six alternating blocks of dasatinib, methotrexate plus asparaginase, and cytarabine. Patients on maintenance therapy receive alternating blocks of dasatinib, mercaptopurine plus methotrexate, and dexamethasone plus vincristine. This study also demonstrated high activity (Table 3), with 33% of patients achieving undetectable levels of BCR-ABL transcripts. MRD continues to decrease with time, and median RFS and OS have not yet been reached. Eight (27%) patients have relapsed, 7 bore the T315I mutation, and 1 acquired F317L. One patient died during induction (invasive aspergillosis), 2 during consolidation (pulmonary embolism and physical deterioration), 1 during maintenance (pneumonia), and 4 have died of relapse.

In patients unable to receive SCT, dasatinib-based treatment may, therefore, provide an effective first-line option. It should also be noted that dasatinib (and nilotinib; see below) has recently been shown to facilitate SCT, without increasing toxicity, in patients with Ph+ ALL, thereby potentially widening the currently small pool of patients eligible for this treatment.⁶⁰

Other Agents

Nilotinib is a second-generation TKI approved for the treatment of patients with chronic-phase/accelerated-phase chronic myelocytic leukemia (CML) who experienced failure on previous therapy, including imatinib. It has not been approved for the treatment of patients with Ph+ ALL. Nilotinib demonstrated activity in patients with Ph+ ALL resistant to imatinib in a phase 1 study (n = 41).⁶¹ At the latest follow-up in a phase 2 study of nilotinib 800 mg/d in this indication, a CHR rate of 24% was reported after median treatment duration of 53 days.⁶² The most common grade 3-4 laboratory abnormalities were thrombocytopenia (60%), neutropenia (43%), anemia (21%), and hypophosphatemia (22%).

Mutagenesis-resistance screening indicates the selection of T315I and P-loop mutations during nilotinib treatment⁶³; as discussed earlier, these mutations are among the most commonly observed in Ph+ ALL. A secondary analysis of patients in the phase 1 study showed that BCR-ABL was reactivated rapidly in patients with progressive disease featuring the P-loop mutations Y253H and E255K (or T315I).⁶⁴

Bosutinib is a novel BCR-ABL/SRK inhibitor in early clinical development for Ph+ ALL. Preliminary data from a study of bosutinib 500 mg/d in patients with advanced or Ph+ ALL who experienced failure on previous imatinib therapy (N = 101) indicate that this drug has activity in patients with Ph+ ALL.⁶⁵

Several agents in an early-stage development exhibit putative activity against T315I; one such compound is homoharringtonine.⁶⁶ The need for such agents is significant, given that all commercially available TKIs are insensitive to this mutation. Indeed, many patients who relapse following dasatinib treatment are found to bear T315I. A combination of dasatinib and a T315I-inhibiting agent may be effective as first-line treatment of Ph+ ALL.

Conclusions

Ph+ ALL was previously associated with an overall poor prognosis. Survival time for patients treated with chemotherapy alone is usually short. Currently, alloSCT remains the treatment of choice but is limited to eligible patients with available appropriate donors. Imatinib has enhanced the benefits of conventional chemotherapy, but many patients who initially respond to treatment with imatinib experience resistance. For patients experiencing resistance or intolerance to imatinib, the development of newer BCR-ABL-targeted TKIs have presented other therapeutic options. Patients who show signs of imatinib failure should, therefore, promptly be offered alternative treatment.

Clinical trials have demonstrated that dasatinib can induce significant activity either as monotherapy or combination partner in both first- and second-line treatment for patients with Ph+ ALL. The continued development and incorporation into first-line therapy of compounds able to inhibit the T315I gatekeeper mutation should further improve outcomes.

Acknowledgments

The author takes full responsibility for the content of this publication and confirms that it reflects his viewpoint and medical expertise. He also wishes to acknowledge StemScientific, funded by Bristol-Myers Squibb, for providing

writing and editorial support. Bristol-Myers Squibb did not influence the content of the manuscript, nor did the author receive financial compensation for authoring the manuscript.

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Table 1

Summary of Clinical Trials of Imatinib and Chemotherapy in Patients With Untreated Ph+ ALL

Reference	N	Median Age (Years)	Median Follow-up (Months)	CR (%)	Relapse (%) ^a	Median OS (Months)
16	20	37	26	95	32	29.4
17, 18	30	66	64	90	15	NR
19	92	46	NR	N/A	2-11	16.3-19.6
20	77	48	13	96	26	NR
21	45	45	NR	96	19	NR
22	267	40	98	82	NR	9
23	20	42	20	100	10	NR

^aDenominator: number of patients who achieved CR. Abbreviations: CR = complete response; N/A = not applicable; NR = not reported; OS = overall survival.

Table 2

Summary of Phase 2/3 Clinical Trials of Dasatinib in Previously Treated Patients With Ph+ ALL

Reference	Median Age (Years)	Minimum Follow-up (Months)	Regimen	N	CR (%)	MCyR (%)	CCyR (%)	MMR (%)	Undetectable MRD (%)	Median PFS (Months)	Median OS (Months)
53	46	24	Dasatinib 70 mg twice daily	46	35	56	54	NR	NR	3.3	NR
55	46	24	Dasatinib 70 mg twice daily	44	25	52	39	NR	NR	3.1	9.1
			Dasatinib 140 mg once daily	40	33	70	50	NR	NR	4.0	6.5
56	49	NR	Dasatinib 70 mg twice daily plus chemotherapy ^a	23	65	90	74	65	44	NR	9.0

^aSee text. Abbreviations: CR = complete response; CCyR = complete cytogenetic response; MCyR = major cytogenetic response; MMR = major molecular response; MRD = minimal residual disease; NR = not reported; OS = overall survival; PFS = progression-free survival.

Table 3

Summary of Phase 2/3 Clinical Trials of Dasatinib in Untreated Patients With Ph+ ALL

Reference	Median Age (Years)	Median Follow-up (Months)	Regimen	N	CR (%)	MCyR (%)	CCyR (%)	MMR (%)	Undetectable MRD (%)	24-Month PFS (%)	24-Month OS (%)
57	54	11	Dasatinib 70 mg twice daily	34	100	NR	NR	NR	NR	NR	NR
58	53	14	Dasatinib 70 mg twice daily plus chemotherapy*	35	94	NR	86	77	57	57	64
59	71	12	Dasatinib 100-140 mg once daily plus chemotherapy ^a	30	97	NR	NR	NR	33	NR	NR

^aSee text. Abbreviations: CR, complete response; CCyR, complete cytogenetic response; MCyR = major cytogenetic response; MMR = minimal residual disease; MRD = not reported; OS = overall survival; PFS = progression-free survival.