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REVIEW

The Role of Imatinib in Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia

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Abstract: Incorporation of imatinib, a BCR-ABL tyrosine kinase inhibitor, into treatment regimens for Philadelphia-chromosome positive acute lymphoblastic leukemia (ALL) has improved outcomes. Single agent therapy, as well as imatinib in combination with chemotherapy demonstrates high response rates, however durable remissions are rare due to rapid development of resistant disease. The only potentially curative option is stem cell transplant, which remains the recommendation for eligible patients in first complete remission. Significant challenge lies in recognizing and overcoming kinase domain mutations. Second generation tyrosine kinase inhibitors can overcome a majority of imatinib resistant mutations and inclusion of these agents will be integrated into future treatment regimens.

Keywords: imatinib, acute lymphoblastic leukemia, ALL, Philadelphia-chromosome

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Acute lymphoblastic leukemia (ALL) is characterized by the expansion and proliferation of lymphoid cells in the bone marrow, blood, and other organs. ALL is the most common type of cancer in children aged 0–14 years.[1] ALL is relatively uncommon in late childhood, adolescence, and young adulthood. Though treatment advances have led to survival rates above 80% in children, comparable outcomes have not yet been achieved in adult patients with ALL. The identification of molecular subtypes led to the addition of targeted therapy as a means to improve survival in specific groups of ALL.

Several factors have been identified that aid in prognostic determination. Older age, high leukocyte count, immunophenotype other than T cell, Philadelphia chromosome positivity, and longer time to achieve initial complete remission (CR) have all been associated with poor prognosis.[2] Associations with poor performance status, organomegaly, low platelet counts, low albumin levels, and elevated serum lactate dehydrogenase have also been indicative of poor prognosis. Survival of relapsed patients is adversely effected by short duration of CR.[3,4] Increased bone marrow blasts, thrombocytopenia, hypoalbuminemia, female sex, older age, and site of relapse have also been recognized as poor prognostic factors in relapsed ALL.

The Philadelphia chromosome occurs from a translocation between the long arms of chromosome 9 and 22, creating the hybrid gene *BCR-ABL*.[5] The molecular weight of this protein product depends on the location of the breakpoint, with the majority of patients with ALL expressing the 190 kDa oncoprotein ($p190^{bcr\text{-}abl}$), and the remainder characterized by the 210 kDa oncoprotein ($p210^{bcr\text{-}abl}$), commonly displayed in chronic myeloid leukemia (CML).[6] Philadelphia chromosome-positivity (Ph-positive) is the most common cytogenetic abnormality in adults with ALL, occurring in 20%–30% of patients.[7–8] The outcome of patients with Ph-positive ALL treated with conventional chemotherapy traditionally remains poor with long term disease free survival less than 10%, mostly due to low CR rates and short remission duration. The incorporation of targeted therapy using tyrosine kinase inhibitors increased response rates, however maintaining remission remains challenging due to relapse associated with mutations in the bcr-abl kinase domain.[9] Therefore, allogeneic stem cell transplant (SCT) is recommended for all patients with Ph-positive ALL who achieve CR.

The introduction of imatinib revolutionized the management and improved the prognosis of patients with CML. The role of imatinib, as well as second generation tyrosine kinase inhibitors (TKIs) remains under evaluation in Ph-positive ALL. Synergistic effects are possible with the addition of TKI's to chemotherapy including anthracyclines, vincristine, and cytarabine. While the optimal schedule of tyrosine kinase inhibitors has yet to be determined in ALL, early initiation and prolonged treatment courses have been implicated to provide the best outcomes.

Imatinib: Single Agent Therapy

Poor prognosis with elderly patients is attributed to increased potential for hematologic and non-hematologic toxicity that may increase induction mortality or compromise compliance with chemotherapy.[10] Disease refractory to standard chemotherapy is an additional element of consideration. Although SCT improves long term survival in Ph-positive ALL, elderly patients are likely excluded from this option. Lower intensity therapy that specifically controls leukemia cell proliferation may improve outcomes and decrease treatment related mortality. Imatinib, a selective TKI that binds to BLR-ABL in the closed conformation, halts the signal transduction cascade and activity of downstream targets.[11] Monotherapy was initially evaluated in relapsed patients as well as newly diagnosed elderly patients (Table1). Druker and colleagues demonstrated that single agent imatinib displayed activity in CML blast crisis and relapsed/refractory ALL at doses ranging from 300–1000 mg per day.[12] Of the patients with either lymphoid blast crisis or Ph+ ALL, 70% achieved a response, with 20% attaining CR. Although patients with lymphoid blast crisis generally sustain responses to standard chemotherapy, the use of imatinib in this study trended towards more durable responses in myeloid blast crisis. Sustained hematologic response and safety were further evaluated in patients with relapsed Ph-positive ALL treated with doses of imatinib ranging from 400 mg to 600 mg per day by Ottmann and colleagues. Of 48 patients, hematologic response lasting 4 or more weeks in duration was attained in 27% with a median time to progression of 2.2 months with an estimated overall survival of

Table 1. Single agent investigation of imatinib in Ph-positive ALL.

Study	Patient population	Median age in years (Range)	Number of patients (n)	OR (%)	CR (%)
Druker et al[12]	Relapsed/refractory	48 (24–76)	20	70	20
Ottmann et al[13]	Relapsed/refractory	50 (22–78)	48	60	19
Wassman et al[14]	Relapsed/refractory	48 (17–76)	68	70	30
Ottmann et al[15]	Newly diagnosed				
Imatinib		66 (54–79)	28	100	96
Chemotherapy		68 (58–78)	27	58	50
Vignetti et al[16]	Newly diagnosed	69 (61–83)	30	100	100

4.9 months.[13] Time to disease progression is improved by early response to treatment with imatinib.[14] Factors negatively affecting response, time to progression, and overall response include the presence of the Philadelphia chromosomes or at least 2 additional Bcr-Abl fusion signals at time of relapse.

In newly diagnosed elderly patients, imatinib displayed significantly superior responses with limited morbidity and mortality compared with intensive chemotherapy.[15] A German study randomized patients aged 55 years or older with de novo Ph-positive ALL or CML in first lymphoid blast crisis to receive imatinib 600 mg per daily or multiagent chemotherapy. Both groups received identical central nervous system prophylaxis with intrathecal chemotherapy. Of the evaluable patients, 28 assigned to imatinib and 27 assigned to multiagent chemotherapy, the overall CR rate in the imatinib arm was 96%, of which 85% achieved CR and 11% attained CR without peripheral blood count recovery, while the overall CR rate in the induction chemotherapy arm was 50%, with the majority represented as CR without peripheral blood count recovery. The combination of imatinib plus steroids produced encouraging results in elderly patients with Ph-positive ALL in a study by Vignetti and colleagues.[16] Of 29 patients evaluable for response, 100% achieved CR after a 45-day induction period of imatinib 800 mg per day in combination with prednisone. However, after 10 months follow-up, only 13 patients remained alive and in complete remission. Although imatinib without chemotherapy provides an option for patients unable to tolerate intensive induction therapy, long term disease free survival and overall survival remain poor, with many patients relapsing from their disease. Furthermore, it is unlikely that single agent imatinib will provide adequate survival benefit.

Imatinib Based Chemotherapy Combinations

A substantial amount of data exists investigating imatinib in combination with chemotherapy, with the majority of these evaluations in younger patients considered fit to tolerate induction chemotherapy. The incorporatation of imatinib with chemotherapy has been approached with concurrent administration (administration at the same time) and sequential administration (alternating administration). Concurrent administration

Table 2. Imatinib based chemotherapy combinations in Ph-positive ALL.

Study	Patient population	Chemotherapy regimen	Number of patients (n)	CR (%)
Thomas et al[6]	Newly diagnosed	Hyper-CVAD	15	100
Thomas et al[17]	Newly diagnosed	Hyper-CVAD	43	91
Towatari et al[18]	Newly diagnosed	ALL202	24	96
Delannoy et al[19]	Newly diagnosed	AFR09	30	70
de Labarthe et al[21]	Newly diagnosed	GRAAPH-2003	45	96
Rea et al[46]	Relapsed/refractory	DIV	18	94

Note: DIV: dexamethasone, imatinib, vincristine.

was initially evaluated with hyper-CVAD.[6] During induction and consolidation therapy, imatinib 400 mg per day was administered for 14 days concurrently with hyper-CVAD. Imatinib, 600 mg per day administered continuously, combined with vincristine and prednisone comprised the maintenance regimen, with higher dose imatinib owing to the absence of myelosuppressive chemotherapy. A total of 20 patients were enrolled for evaluation, 15 with active disease and 5 in CR previously treated with non-imatinib based chemotherapy. All patients with active disease at start of therapy achieved CR, of which 93% were reported after one cycle. Fifty percent of patients underwent allogeneic SCT in first CR, with 90% in CR one year post SCT. Further dose modification of imatinib combined with hyper-CVAD improved 3-year remission and disease free survival as compared to hyper-CVAD alone.[17] The JALSG ALL202 Ph-positive arm integrated concurrent imatinib into remission induction therapy.[18] Two separate courses consisting of methotrexate combined with cytarabine and single agent imatinib alternated during consolidation. Of 24 newly diagnosed Ph-positive ALL patients enrolled, 96% achieved CR after one course of induction therapy, and 63% proceeded to allogeneic SCT. However, short duration of follow-up limited the determination of survival benefit. Alternating chemotherapy with administration of imatinib combined with steroids was evaluated in 30 newly diagnosed patients over 55 years of age.[19] Seventy-two percent CR rate was reported following induction chemotherapy, with 5 additional patients reported following completion of imatinib. Compared with similar control patients treated with chemotherapy that did not include imatinib, overall survival as well as relapse free survival was significantly improved in patients that received imatinib.

Concurrent administration of imatinib with chemotherapy has been reported to have more antileukemia efficacy than sequential administration, measured by PCR negativity.[20] Two cohorts of patients were evaluated in the German Multicenter Acute Lymphoblastic Leukemia trial. The initial cohort scheduled imatinib alternating with chemotherapy while the treatment design of the second group involved concurrent administration. BCR-ABL transcripts became undetectable in 52% of patients in the concurrent arm versus 19% receiving sequential therapy, however these results did not result in significant differences in survival. The initiation of earlier versus later imatinib requires further clarification. Good early responders, defined by corticosensitivity and chemosensitivity, were enrolled in the GRAAPH-2003 study during the first course of consolidation therapy.[21] Consolidation consisted of mitoxantrone and cytarabine combined with intrathecal chemotherapy and continuous imatinib dosed at 600 mg daily. Poor early responders, those patients that did not display early corticosensitivity and chemosensitivity, changed from standard induction therapy to imatinib 800 mg per day combined with vincristine and dexamethasone (DIV). CR rate was reported as 96% for all patients enrolled (n = 45). Of the total patients enrolled, 14 were good early responders, indicating imatinib initiation during consolidation. All patients with a donor (n = 22) proceeded with allogeneic SCT, while 6 additional patients underwent autologous SCT. Most recently, the GRAALL enrolled 188 newly diagnosed patients, of which 83 were evaluable at time of report, to compare an imatinib-based induction regimen to imatinib-hyperCVAD induction therapy.[22] Imatinib 800 mg per day combined with vincristine and dexamethasone comprised the imatinib-based arm, while imatinib 800 mg per day on days 1–14 combined with hyper-CVAD made up the second arm of comparison. Preliminary data analysis after two courses of induction/consolidation reported 100% CR rate for the imatinib-based treatment group (n = 42) versus 95% reported for imatinib-hyperCVAD (n = 41). Intensification involved allogeneic or autologous SCT or continued cycles of imatinib-hyperCVAD. Fifty-two patients underwent SCT, 41 allogeneic and 11 autologous. At two years, the overall survival rate reported was 62%, with no significant difference between imatinib-based and imatinib-hyperCVAD treatments.

Stem Cell Transplant (SCT) and Tyrosine Kinase Therapy

The overall prognosis of Ph-positive ALL remains poor. Allogeneic SCT represents the only curable option, however resistant disease creates challenge in attaining CR, and outcomes with relapsed or resistant disease are discouraging. In younger patients, SCT remains the standard of care in first CR. Older patients are generally excluded from this option due to high treatment related morbidity and mortality.

Achievement of CR corresponds with favorable outcomes after allogeneic SCT. Incorporation of imatinib has improved the rate of high quality CR, thus enabling more patients to proceed with SCT. Early remission with imatinib confers durable responses in salvage therapy, with extended time to relapse.[14] Day 14 marrow with reduction of blasts to below 5% was predictive of subsequent marrow and hematologic remissions. Salvage single agent therapy with imatinib enables the majority of patients eligible to undergo SCT. Of 30 relapsed patients administered imatinib 600 mg daily, 73% underwent allogeneic transplant after a median of 53 days of treatment.[23] However, resistance develops readily to single agent imatinib, therefore SCT should be incorporated shortly after CR. In newly diagnosed patients, imatinib in combination with chemotherapy during consolidation therapy allowed for sustained CR and reduction of leukemic burden prior to SCT.[24] SCT was performed in 28 of 29 patients treated with interim imatinib based therapy. Patients received imatinib 400 mg or 600 mg daily in addition to consolidation or salvage chemotherapy, depending on response after the initial induction cycle. Considering the influence of imatinib on engraftment has not been determined, imatinib was discontinued 7 days prior to the conditioning regimen in this study. All patients effectively engrafted. After approximately one year of follow up, 86% were alive post SCT. Long term effects on survival remain to be determined.

Potential responses to imatinib are possible post transplant relapse, however complications from SCT as well as refractory disease limit the use in this setting.[25] Second generation tyrosine kinase inhibitors demonstrate activity, but limited data exists, with the majority represented as case reports. Dasatinib therapy commencing after expression of imatinib resistance post stem cell transplant produced continuous reduction in BCR-ABL transcripts, with sustained remission reported 18 months post transplant.[26] Considering the response demonstrated with imatinib and interferon-α, the substitution for imatinib with dasatinib proved effective in one heavily pretreated patient.[27] A 75 month CR was attained after third relapse with imatinib in combination with interferon-α. Only mild decrease of the BCR-ABL transcript was achieved with treatment of single agent dasatinib during fourth relapse. At time of fifth relapse, interferon-α in combination with dasatinib was initiated. Molecular CR was reported and continued for 13 months at time of publication. Nilotinib has also demonstrated activity in relapsed/refractory Ph-positive ALL, and has been reported to induce CR.[28–30] The use of TKIs maintenance strategy in patients with high-risk disease is currently being assessed.

Imatinib Limitations

Resistance to imatinib develops readily which limits the success of this agent as monotherapy. Acquired resistance to imatinib most commonly results from mutations in the kinase domain of ABL that limits the binding affinity, and BCR-ABL amplification. In CML, kinase domain mutations occur in approximately 45% of patients, presenting after approximately 20–35 months of treatment.[31–33] In patients with ALL, approximately 25%–30% display primary resistance.[13] Secondary resistance occurs rapidly, with an estimated time to development of 2 months after treatment initiation.[13,34] Natural evolution of disease may be responsible for kinase domain mutations in CML, as development can occur regardless of treatment with imatinib.[35] However, in ALL, the majority of mutations are recognized after treatment with a TKI.[36] In Ph-positive patients that were not treated with imatinib, at time of relapse none were noted to have kinase domain mutations.[37] However, of those patients that received therapy including a kinase inhibitor, 88% displayed mutations at time of morphological recurrence, at a median time of 10 months from diagnosis. In comparison with patients receiving intermittent kinase inhibitor therapy, mutations in codons 253 and 315 presented more frequently in patients on continuous treatment.

Approaches to minimize disease resistance may include intermittent therapy with kinase inhibitors, dual therapy with imatinib and advanced generation kinase inhibitors, and addition of agents that suppress clonal evolution. In addition, dose reductions of imatinib should be avoided as this may increase resistance.[34] Nilotinib, a selective Abl inhibitor, displays a higher binding affinity to Bcr-Abl than imatinib. Despite binding to the same site, activity against specific point mutations that confer resistance to imatinib can be achieved with nilotinib. In theory, the combination of these agents can enhance activity

through interactions with cell transporters such as Oct-1, an organic cation transporter, or ABCG2, the multidrug efflux transporter.[38,39] However, combining TKIs is unlikely to be effective against the T315I mutation. Combination therapy with TKIs requires further evaluation, but could serve as a means to enhance activity and minimize kinase domain mutation relapse. Suppression of clonal evolution and immune response stimulation are theoretical reasons for addition of interferon-α with kinase inhibitors. In a small series, imatinib in combination with interferon-α displayed encouraging outcomes.[40] However, the response with immunologic therapy in Ph-positive ALL has historically been disappointing, therefore this data must be confirmed in a prospective evaluation.

In the absence of prophylactic interventions, 50% to 75% of adult patients will develop central nervous system (CNS) relapse within a year.[41,42] Imatinib displays poor penetration into the CNS, providing suboptimal prophylaxis and treatment of CNS disease.[43,44] In one report of a patient with CNS involvement treated with imatinib, concentrations were approximately 92 times lower in the CNS than the peripheral blood. Of note, despite using reduced dose imatinib, therapeutic trough concentrations in the serum were achieved. Since this kinase inhibitor poorly penetrates the blood brain barrier, intrathecal chemotherapy should be incorporated into imatinib containing regimens.

Imatinib: Role in Relapsed/Refractory Disease

Toxicity from previous therapy limits the opportunity for repeated cycles of intensive chemotherapy at time of relapse. Unfortunately, resistance to imatinib develops quickly, limiting its role as monotherapy in relapsed disease, especially for those patients previously treated with this agent. Reports for relapsed or resistant Ph-positive ALL, suggest single-agent imatinib provides adequate responses in patients previously treated with non-imatinib containing therapy.[12–14,16,45] Higher doses in combination with less intensive chemotherapy demonstrated high CR rates, suggestive that more tyrosine kinase inhibition may be beneficial. Regardless of prior treatment, 800 mg per day of imatinib was administered in combination with vincristine and dexamethasone to 31 patients with relapsed or resistant Ph-positive ALL or CML lymphoid blast crisis.[46] Ninety percent CR rate was reported, with major cytogenetic response reached in 16 patients, of which 14 were reported as complete. Though hematologic toxicity was comparable to previous reports with intensive chemotherapy regimens, neuropathy due to vincristine was frequent and required replacement in 29% of patients. The reported CR rate in patients over 55 years of age was 90%, indicating that this low intensity chemotherapy regimen is effective in elderly patients. Prior treatment with imatinib did not significantly impact overall survival, however, those patients not treated with prior imatinib experienced a median 448 days overall survival compared with 222 days in those previous treated with imatinib.

The primary disadvantage of imatinib in relapsed Ph-positive ALL can be attributed to secondary resistance acquired from kinase domain mutations, implying that perhaps imatinib was not utilized correctly in front line therapy. With a large majority of institutions now including imatinib at some point during initial therapy, approaches for overcoming imatinib resistance at time of disease recurrence must be further explored. Second generation TKIs at time of relapse remain under evaluation. As an alternative, inclusion of these agents into front-line therapy may improve outcomes and their impact on survival has yet to be confirmed.

Future Directions

The results of studies involving second generation kinase inhibitors in Ph-positive ALL pave the way for alternative regimens. START-L evaluated single agent dasatinib administered at time of relapse in pre-treated patients.[47] Dasatinib 70 mg twice daily was administered continually with dose escalations permitted for lack of response and dose reductions allowed for toxicity. Rapid disease control was evident through major hematologic response achieved at a median of 1.8 months. Of 36 patients enrolled in the study, major hematologic response rate was reported for 42%, of which 11 patients achieved complete hematologic response. Complete cytogenetic response rate was reported for 58% of patients and sustained through 8 months of follow-up. The GIMEMA LAL

1205 protocol evaluated single-agent dasatinib in combination with intrathecal chemotherapy.[48] Thirty-four patients were evaluable for response at time of report. Complete hematologic response rate was reported for all patients, with the majority reported at day 22 assessment. Leukemic cell clearance, measured by minimal residual disease, was rapid, especially in the subset of patients displaying the p190 oncoprotein.

Ongoing studies are evaluating the role of dasatinib in combination with chemotherapy in newly diagnosed as well as relapsed and refractory patients (Table 3).[49–51] In newly diagnosed elderly patients aged 55 years and above, dasatinib 140 mg daily was incorporated into induction chemotherapy consisting of weekly vincristine and dexamethasone.[49] Consolidation included cycles of methotrexate and asparaginase alternated with cytarabine, administered with dasatinib 100 mg daily. Dasatinib was also incorporated into maintenance therapy. The complete hematologic response rate reported was 95% (n = 22). A total of four deaths occurred during study, one during induction and three in CR. A high rate of serious adverse events occurred, suggesting dose reductions for patients over 70 years of age. The hyper-CVAD regimen plus dasatinib reported 95% CR in newly diagnosed Ph-positive ALL patients.[50] Fourteen days of dasatinib 100 mg was included with each cycle of induction and consolidation. Continuous dasatinib was included in the maintenance phase of treatment. Of 39 patients evaluable, complete cytogenetic remission was documented in 79% after one treatment cycle. Fifty-six percent of patients have achieved a complete molecular remission. The same regimen was applied to 23 patients with relapsed Ph-positive ALL or CML lymphoid blast crisis.[51] Fifteen patients achieved CR with 6 additional patients achieving CR with incomplete platelet recovery (CRp). Major cytogenetic response was apparent in 19 patients, of which 17 had complete cytogenetic response. Major molecular response was evident in 15 patients, with complete molecular remission present in 10 patients.

Conclusion

Presence of the Philadelphia chromosome confers poor prognosis in ALL patients. The introduction of imatinib has produced striking improvements in response rates in comparison to the pre-imatinib era of treatment. With imatinib more patients achieve high quality CR rates, increasing eligibility for transplant and likelihood of positive outcomes post SCT. Imatinib in combination with low intensity chemotherapy should be recommended for elderly patients. Resistance to imatinib occurs rapidly after treatment initiation, ultimately leading to relapse in a majority of patients. Therefore, new efforts must address overcoming imatinib resistance. Alternative approaches should include dual TKI therapy, second generation TKIs in combination with chemotherapy, and addition of agents that can suppress clonal evolution. Through further understanding the disease process and mechanisms

Table 3. Ongoing adult Ph-positive ALL studies.

Study group	Patient population	Regimen	Number of patients (n)	Preliminary results
EWALL[49]	Newly diagnosed	Dasatinib + chemotherapy	22	CHR 95.2%
EWALL-Ph-01				SAE: 40%
GRAALL[22]	Newly diagnosed	Imatinib-based	42	CR 100%
GRAAPH-2005		hyper-CVAD + imatinib	41	2 year OS 68% CR 95%
				2 year OS 54%*
MDACC[50]	Newly diagnosed	Hyper-CVAD + dasatinib	41	CR 95%**
2006-0478				
MDACC[51]	Relapsed	Hyper-CVAD + dasatinib	23	CR 65%
				CRp 26%

Note: EWALL, European Working Group on Adult ALL; CHR, complete hematologic response; SAE, serious adverse event; GRALL, Group for Research on Adult Acute Lymphoblastic Leukemia; CR, complete remission; OS, overall survival; MDACC, MD Anderson Cancer Center; CRp, complete response without platelet recovery.
*OS reported was achieved with hyper-CVAD + imatinib and SCT.
**CR includes patients treated with one cycle or therapy or in CR at start of therapy.

of resistance, advancements in targeted therapy will improve outcomes in this subset of patients.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

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