Acute Lymphoblastic Leukemia in Adults

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Treatment of Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia

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Philadelphia chromosome positive (Ph⁺) acute lymphoblastic leukemia (ALL) includes at least one-quarter of all adults with ALL. Until recently, conventional chemotherapy programs that have been effective in other precursor B-cell ALL cases have been unable to cure patients with this diagnosis. Allogeneic stem cell transplantation early in first remission has been the recommended therapy. The availability of imatinib mesylate and other tyrosine kinase inhibitors and small molecules that affect the *BCR/ABL* signaling pathways may be changing the treatment paradigm and the prognosis for these patients. The results from clinical trials using imatinib in the frontline setting and in relapsed patients as well as preliminary experience treating imatinib-resistant Ph⁺ ALL will be described.

Clinical Features of Ph⁺ ALL

The Philadelphia chromosome (Ph), the result of a reciprocal translocation fusing the abl proto-oncogene from chromosome 9 with the breakpoint cluster region sequences on chromosome 22, was the first cancer-specific translocation to be identified.[1] Translocation (9;22) is the most frequent genetic aberration in adult acute lymphoblastic leukemia (ALL) and is found in 20%-30% of patients overall; it increases with age, approaching 50% in patients older than 50 years.[2,3] In past clinical studies, older patients were underrepresented due to the perceived futility of treatment, but this pattern is changing with the availability of the promising novel treatment options discussed in this review. Notably, it is found almost exclusively in CD10⁺ precursor B-cell ALL (c-ALL and pre-B ALL); rare reports of its presence in T-lineage ALL may represent chronic myeloid leukemia (CML) in lymphoid blast crisis rather than *bona fide* Ph⁺ ALL. Clinically, patients present with a variable WBC count, surface expression of CD19, CD10 and CD34 anti-

gens, and frequent coexpression of myeloid markers, e.g., CD13 and CD33. Patients have an increased risk of developing meningeal leukemia during the course of treatment, although CNS leukemia is not significantly more frequent at diagnosis.[2,4]

The principles of initial diagnosis are the same as for ALL in general, relying on cytology and immunophenotyping by flow cytometry. Cytogenetic and molecular genetic analyses are required to establish the diagnosis of Ph⁺ ALL and can generally be obtained within one week of diagnosis. The diagnosis of Ph⁺ ALL should be considered in all patients with precursor-B ALL, particularly in older patients and those coexpressing myeloid markers. Given the options of targeted therapy discussed below, considerable efforts should be directed at obtaining the results of molecular genetic analyses as early as possible.

Chemotherapy for Newly Diagnosed Ph⁺ ALL

The prognosis of adult patients with Ph⁺ ALL treated only with chemotherapy is poor, with a less than 10% probability of long-term survival. Before targeted treatment with the Abl-kinase inhibitor imatinib became available, complete remission (CR) rates after induction chemotherapy in younger patients ranged from 60%-90%, moderately lower than the 70%-90% achieved in Ph-negative ALL. The median CR duration was considerably inferior, however, ranging from 9-16 months in patients treated only with chemotherapy, with almost no long-term survivors.[2-7]

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Stem Cell Transplantation

Because of the dismal outcome with chemotherapy, allogeneic stem cell transplantation (SCT) is considered to be the treatment of choice in adult Ph⁺ ALL. Twenty-seven to 65% long-term survival has been reported for patients undergoing SCT in first complete remission (CR1), indicating that this procedure is potentially curative.[8] Unfortunately, approximately 30% of patients experience relapse, making this the most frequent cause of treatment failure next to treatment-related mortality (TRM), which increases with age and advanced disease.[8,9] Beyond first remission, SCT is curative in only a small minority of patients but remains the treatment of choice: the probability of disease-free survival (DFS) at 2 years after allogeneic SCT in second or third remission or as salvage therapy for refractory disease has been reported to be 17% and 5%, respectively.[10] In patients failing allogeneic SCT, further treatment is rarely successful.

Few long-term results of autologous SCT in Ph⁺ ALL are available; in the largest series so far reported, the use of purged bone marrow or peripheral blood stem cells resulted in leukemia-free survival of 22% after a median of 52 months. However, none of the patients transplanted beyond CR1 survived long-term.[11]

Imatinib in Ph⁺ ALL

Imatinib in refractory Ph⁺ ALL

Elucidation of the leukemogenic role of the Bcr/Abl oncogene in Ph⁺ leukemias and its dependency on the constitutive activation of the ABL tyrosine kinase prompted the development of selective ABL inhibitors.[12] Imatinib was the first such compound to gain clinical approval. The encouraging results obtained with imatinib in CML prompted initiation of several phase I and II studies in patients with relapsed or refractory Ph⁺ ALL.[13-15] Approximately 60% of patients achieved a remission or clearance of peripheral blood blasts, with 19% CR. Disappointingly, these responses were short lived with median time to progression and overall survival of only 2.2 and 4.9 months, respectively.[14] Only the subset of patients undergoing allogeneic SCT while still in remission had a favorable outcome, with 51% DFS after 1 year.[34]

The poor results of single-agent imatinib in advanced Ph⁺ ALL led various investigators to explore the efficacy of imatinib as front-line treatment of Ph⁺ ALL.

Imatinib in combination with chemotherapy

The administration of imatinib in addition to induction and consolidation chemotherapy for newly diagnosed Ph⁺ ALL was anticipated to enhance antileukemic efficacy and prevent the development of secondary resistance. Updated results of a phase II study combining imatinib (days 1–14 of each cycle) with hyperCVAD chemotherapy in Ph⁺ ALL patients were reported by Thomas et al.[16] Twenty-five of 26 patients (96%) with active disease at study entry achieved

a CR after a median of 21 days, suggesting synergy between imatinib and concurrent chemotherapy. Molecular response, defined as negative bone marrow RT-PCR for bcr-abl confirmed by nested PCR, was achieved in 5 patients after hyperCVAD and imatinib alone and another 12 after allogeneic SCT. There were no unexpected toxicities related to the addition of imatinib. Similarly encouraging results were observed in a prospective study conducted by the Japanese Adult Leukemia Study Group, in which imatinib was started after one week of induction therapy and then coadministered with chemotherapy during the remainder of the induction.[17] During consolidation, imatinib was alternated with high-dose methotrexate/cytarabine. The CR rate was 95%, and a remarkably high molecular response rate became apparent as early as 2 months after starting treatment, reaching 73% after more prolonged therapy. The 1-year event-free survival (EFS) and overall survival (OS) rates were estimated at 78% and 88%. Tolerability was not distinguishable from that observed with chemotherapy alone.[17] The combination of imatinib with a wide variety of cytotoxic agents was also studied in the Spanish PETHEMA and GETH protocols. Parallel administration of imatinib with induction and consolidation chemotherapy was tolerated and the CR rate approached 90%,[18] in good agreement with the studies cited above. Subsequent stem cell transplantation did not appear to be adversely affected by preceding imatinib therapy in any of these studies.

The optimal schedule for combining imatinib with chemotherapy has not been established. Alternating and concurrent imatinib/chemotherapy combinations were compared in two sequential patient cohorts treated within a recent German GMALL trial. Efficacy analyses based on bcr/abl transcript levels showed a clear advantage of the simultaneous over the alternating schedule, with approximately 50% of patients achieving PCR negativity. Both schedules enabled a high percentage of patients to undergo stem cell transplantation, with no apparent detrimental effect of prior imatinib.[19]

Single-agent imatinib as up-front treatment in older patients with Ph⁺ ALL

Chemotherapy in elderly Ph⁺ ALL patients is associated with an exceptionally poor prognosis due to a low CR rate, short remission duration and high induction mortality.[4] Treatment intensification in these patients is often limited by comorbidity. In view of the favorable toxicity profile of imatinib, several studies explored the value of single-agent imatinib induction therapy in elderly patients with newly diagnosed Ph⁺ ALL. In an Italian GIMEMA study, 12 patients ≥ 61 years received imatinib at 800 mg/day in combination with prednisone for 30 days, without any other chemotherapy, followed by imatinib monotherapy as post-remission treatment. Ninety-two percent of patients achieved a CR, with 8 patients (67%) in CR after a median follow-up of 7 months.[20]

The GMALL evaluated imatinib monotherapy as in-

duction for de novo Ph[+] ALL in a prospective, randomized multicenter trial.[21] Elderly patients (median age, 67 years) were randomly assigned to receive a 4-week course of imatinib at 600 mg/day or induction chemotherapy. Patients completing induction with a CR or partial remission (PR) then received imatinib concurrently with consolidation and reinduction cycles. Imatinib induction was significantly superior to chemotherapy, with 93% and 7% of patients achieving a CR or PR, respectively, for an overall response rate of 100%. In contrast, 46% of evaluable patients allocated to the chemotherapy arm failed treatment. Severe infectious complications were less frequent in patients allocated to imatinib induction, with no induction mortality.[21]

Consolidation with imatinib plus chemotherapy

Low or undetectable bcr-abl transcript levels prior to allogeneic SCT are favorable risk factors in patients with Ph[+] ALL. Adding imatinib to consolidation chemotherapy may increase the proportion of PCR negative patients and decrease the relapse rate prior to SCT. In a phase I/II study, increasing dosages of imatinib were combined with intermediate-dose cytarabine and mitoxantrone (HAM). Preliminary results demonstrated an excessive toxicity in the imatinib 800 mg/d cohort. Combination studies employing imatinib at 600 mg/d did not show an improved molecular response rate compared with a historical control, suggesting that imatinib may be more effective if incorporated during the first induction cycle.[22]

A similar treatment approach for elderly patients with newly diagnosed Ph[+] ALL was evaluated in the French GRAALL AFR09 trial recently reported by Delannoy et al. Induction chemotherapy is followed by imatinib plus successive short dexamethasone pulses over a 2-month period. Subsequent consolidation therapy consists of alternating chemotherapy cycles and two 2-month blocks of imatinib and CNS-directed prophylactic therapy.[23] In an interim analysis, the high CR rate and survival probability are encouraging and suggest that the combination of imatinib with short dexamethasone may enhance anti-leukemic efficacy without aggravating toxicity.

Stem cell transplantation after front-line imatinib

The feasibility of performing allogeneic SCT after first-line imatinib plus chemotherapy in newly diagnosed Ph+ ALL was reported by Lee et al.[24] Twenty-nine adult patients who completed induction chemotherapy underwent allogeneic SCT, and the results were compared with those in 31 historic patients who proceeded to allogeneic SCT without imatinib therapy. Relapse during the post-remission treatment phase prior to SCT was significantly less frequent in the imatinib group (3.5% vs 42.3%, $P = 0.002$). Accordingly, a greater proportion of patients in the imatinib were transplanted in sustained CR. This translated into lower relapse and superior DFS (76% vs 38%, $P = 0.001$) for the imatinib group. Acute transplant-related toxicity and mortality were not different in the two groups. These results suggest that imatinib interim therapy might improve the curative potential of SCT in Ph[+] ALL.[24]

Mechanisms of resistance to imatinib

Clinically, "primary resistance" is a failure to achieve a CR and can be distinguished from "secondary resistance" that arises in patients with imatinib-induced complete remission who relapse despite continued imatinib treatment. Mechanisms that have been implicated in resistance include rapid drug efflux, reduced binding affinity of imatinib to the ATP-binding site due to genetic changes, and BCR-ABL independence resulting from secondary transforming events. As in chronic myeloid leukemia (CML), secondary resistance in Ph[+] ALL is frequently associated with point mutations in the tyrosine kinase domain (TKD) of bcr-abl, which interfere with imatinib binding to the enzyme.[25-26] The frequency and the distribution of abl TKD mutations in patients with Ph[+] ALL remain uncertain because the number of patients investigated is small. In rare cases, the mutation present at the time of relapse was shown to pre-exist in a subpopulation of leukemic cells prior to imatinib treatment.[27]

Central Nervous System–Directed Prophylactic Therapy

Patients with Ph[+] ALL are at significant risk of developing central nervous system (CNS) leukemia. Imatinib concentrations in cerebrospinal fluid have been shown to reach approximately 1%-2% of serum levels and are thus clearly subtherapeutic.[28] Prophylactic intrathecal CNS prophylaxis should therefore be an integral part of any imatinib-based treatment strategy for Ph[+] ALL or CML in lymphoid blast phase (CML-LBP).

Clinical Implications of Minimal Residual Disease

Detection of minimal residual disease (MRD) in patients with Ph[+] ALL is associated with a high probability of relapse.[29] The ability of imatinib to decrease the relapse incidence when initiated in the setting of MRD after SCT was explored in a prospective multicenter phase II study. Initiation of imatinib therapy was triggered by the detection of bcr/abl transcripts at any time after SCT. Twenty-nine patients were enrolled and received imatinib at an initial dose of 400 mg. Bcr/abl transcripts became undetectable by both quantitative and nested RT-PCR in 52% of patients, within a median of 1.4 months. Remissions were sustained in nearly all of these patients. In contrast, patients in whom MRD persisted after a 6-10 week imatinib trial period were almost certain to relapse.[30] Donor lymphocyte infusions were given in addition to imatinib in a small number of patients but did not prevent relapse.

Among non-transplanted patients, obstacles to treating MRD include decreased tolerance of drug and associated medical comorbidity in the elderly population. A GIMEMA study explored the utility of administering imatinib (800 mg/d) without chemotherapy as consolidation

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therapy in patients who had already achieved a CR. Remarkably, 11 of 15 PCR-positive patients remain in CR, as well as all 7 of the enrolled patients who were already PCR negative before study entry.[20]

Low-dose interferon (IFN)-α therapy has shown efficacy in maintaining morphological and cytogenetic remissions after autologous stem cell transplantation or during standard maintenance chemotherapy in patients with Ph[+] ALL. More recently, imatinib in combination with low-dose IFN-α (3 × 1 MU/week) was reported to induce and maintain a complete morphological, cytogenetic and molecular remission in a Ph[+] ALL patient in imatinib-refractory third relapse.[31] In a small series of 6 patients with Ph[+] ALL who were ineligible for SCT, we added low-dose IFN-α to ongoing imatinib in the setting of minimal residual disease (MRD[+]) ($n = 5$) or refractoriness to imatinib ($n = 1$). Four of the 5 MRD[+] patients were alive after a median treatment duration of 15 (11-16) months, with 2 of these patients in hematologic and molecular remission after 15 and 11 months, respectively.[32] Taken together, these results indicate that imatinib in combination with low-dose IFN-α may support prolonged hematologic and molecular remissions in a subset of patients with advanced Ph[+] ALL who are not candidates for allogeneic SCT.

Management of Relapsed or Refractory Ph[+] ALL

Recurrence of Ph[+] ALL is a major therapeutic challenge. Although the probability of success is limited, allogeneic SCT should be considered as it may be curative in a subset of patients.[33] Achievement and maintenance of a CR prior to SCT is a prerequisite for a favorable outcome after SCT.[34] The initial management approach in a Ph[+] ALL patient failing prior therapy needs to consider eligibility for SCT and availability of a suitable donor within a short time period, availability of autologous stem cells and a possible history of a prior SCT. Additional obstacles that often preclude successful SCT are severe treatment-related toxicity and mortality. Presently, most patients with relapsing Ph[+] ALL are likely to have received, and failed, prior imatinib treatment. In this setting, Ph[+] ALL usually follows a rapid and aggressive course. The best type of initial salvage therapy for patients who fail imatinib-based treatment has not been established, but at present it seems most reasonable to enroll these patients in clinical trials. Phase II studies of two novel second generation abl tyrosine kinase inhibitors (AMN107 and BMS354825, see below) are ongoing. The ultimate goal should be to prepare the patients for alloSCT if they are eligible and a remission can be achieved. Diagnostic procedures at relapse should include an evaluation for bcr-abl tyrosine kinase domain mutations, as the presence of the T315I mutation in the majority of leukemic cells will make a response even to these new inhibitors unlikely. Remissions may also be achieved using high-dose chemotherapy with stem cell support in patients with previously collected autologous stem cells. Conventional chemotherapy regimens may be successful, particularly in patients with a more prolonged prior remission duration.[33]

Novel Strategies and Perspectives

The use of imatinib as part of front-line treatment and in combination with cytotoxic agents have greatly improved the rates of complete hematologic and molecular remission and overall outcome in adult patients with newly diagnosed Ph[+] ALL. In addition, several novel kinase inhibitors with significantly more potent antileukemic activity against Bcr-Abl–positive leukemias than imatinib have been developed. Two compounds that have entered phase I and II clinical trials with very promising results are AMN107 and BMS354825.[35,36] AMN107 is a novel ATP-competitive inhibitor of Bcr-Abl that was developed by modifying the aminopyrimidine backbone of imatinib, whereas BMS-354825 is a dual SRC/ABL kinase inhibitor. Both agents have substantially greater potency than imatinib in vitro and in vivo, and are active against the vast majority of BCR-ABL mutants known to confer resistance to imatinib.[35,36] Both compounds appear to be well tolerated and show clinical activity in patients with imatinib-resistant Ph[+] leukemias, but data on clinical efficacy in Ph[+] ALL are still limited.[37,38] Phase II studies of both agents are ongoing; moreover, these compounds are intriguing candidates for combination therapy with other targeted agents that have shown preclinical activity against Ph[+] leukemias, e.g., farnesyl-transferase inhibitors[39] or inhibitors of the PI3-kinase,[40] among others. While allogeneic SCT at present still has to be considered the only treatment option with definite curative potential, clinical and research tools to improve existing and develop novel treatment strategies are rapidly evolving.

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