Ph+Acute Lymphoblastic Leukemia: Use of Tyrosine Kinase Inhibitors

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Abstract
Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) has historically been one of the most difficult to treat subsets of childhood ALL. Based on knowledge of the molecular genetics and biology of BCR-ABL1 fusion produced by the Ph+ in chronic myelogenous leukemia (CML) and Ph+ ALL, first (imatinib) and second (dasatinib and nilotinib) generation tyrosine kinase inhibitors (TKI) that target BCR-ABL1 were developed. These TKIs have revolutionized treatment of CML, and recent studies show that addition of imatinib to intensive chemotherapy leads to dramatic improvements in outcome of pediatric Ph+ ALL. These studies call for a reassessment of the routine use of stem cell transplantation (SCT) for all children with Ph+ ALL. The second generation TKIs have theoretical advantages over imatinib, but have not yet been used extensively in Ph+ ALL. In coming years, studies will define the optimal use of chemotherapy, SCT, and TKI in Ph+ ALL. New agents are being developed to circumvent resistance to first and second generation TKIs in Ph+ ALL and will likely be integrated into future treatment regimens for Ph+ ALL.

Identification of the Philadelphia chromosome and BCR-ABL1 fusion

The Philadelphia chromosome (Ph) was first recognized as a small chromosome present in two patients with CML by Nowell and Hungerford in 1960, and then shown by Janet Rowley in 1973 to be the reciprocal translocation t(9;22)(q34;q11.2). In the early 1980s, molecular investigations revealed that the chromosome 9 gene involved in this translocation was ABL1, (3) the human homologue of the Abelson murine leukemia virus, and that chromosome 22 genomic breakpoints were clustered within a region of 5.8 kilobases (kb) in what was subsequently called the Breakpoint Cluster Region gene (BCR). (4) Subsequent studies showed that the t(9;22) created chimeric BCR-ABL1 transcripts that encoded for a fusion protein of 210 kD that had tyrosine kinase activity. (5) Transgenic mice that expressed BCR-ABL1 were generated and shown to have a myeloproliferative disorder similar to human CML. (6, 7) Critically, parallel studies established that the transforming potential of BCR-ABL1 was entirely dependent on an intact kinase domain. (8)

Development of imatinib and early testing in CML

Taken together, these observations suggested that agents that inhibited the tyrosine kinase activity of BCR-ABL1 might have therapeutic potential for CML. Brian Druker teamed with scientists at Ciba-Geigy (now Novartis) who were screening compounds to identify TKI. This collaboration eventually led to identification of STI571 (imatinib mesylate), which was found to be a potent and specific inhibitor of BCR-ABL1 that could kill CML cells in vitro. (9) A phase I dose escalation study of imatinib in patients with CML refractory to other therapies was begun in 1998. (10) Toxicity was mild in comparison to standard cytotoxic drugs and a maximally tolerated dose (MTD) was not identified when doses of up to 1000 mg/day were tested. The results of this trial were remarkable, with 98% (53/54) of patients with CML in chronic phase (CP) that were resistant/intolerant to interferon attaining a complete hematological response (CHR) when treated with at least 300 mg/day imatinib and 60% had a decrease of Ph+ metaphases to less than 35%. (10) This and other studies led to FDA approval of imatinib for the treatment of CML in 2000, and randomized trials showed imatinib to be the best available first line therapy for patients with CML-CP. (11)
Second generation Abl kinase inhibitors

A number of subsequent studies have shown that patients with CML can develop resistance to imatinib mediated by over-expression of BCR-ABL, or, more commonly, by point mutations in the Abl kinase domain that interfere with imatinib binding.(12) Two second generation Abl class TKIs have been developed to circumvent resistance—dasatinib and nilotinib. Similar to imatinib, nilotinib (formerly termed AMN107) binds only to the Abl class, KIT, and platelet derived growth factor receptor (PDGFR) TKs, but is 10- to 30-fold more potent than imatinib against BCR-ABL1 mutants resistant to imatinib, with the prominent except of the T315I mutation.(13) One of the most closely related kinases to Abl is Src, but imatinib and nilotinib do not inhibit Src kinase activity. Dasatinib, which was originally developed as a SRC kinase inhibitor, was found to be a potent inhibitor of BCR-ABL1 kinase activity (325 times more potent than imatinib in vitro), and active against most imatinib-resistant BCR-ABL1 mutants, again with the exception of T315I.(14) Both dasatinib and nilotinib are now FDA-approved for the treatment of patients with CML who are resistant to, or intolerant of, imatinib, and trials comparing these agents to imatinib are underway in CML.

Treatment of Ph+ ALL in the pre-imatinib era

In addition to its involvement in CML, the Ph+ also occurs in patients with acute lymphoblastic leukemia (ALL), although the genomic breakpoints are typically different leading to production of a 190 kD fusion protein in most cases. The Ph+ is present in about 3% of children with ALL, about 90% of whom have the “ALL type” breakpoints that produce p190 BCR-ABL1.(15,16) The incidence of Ph+ ALL begins to increase in adolescence and the overall incidence in adults is 15-25% with rates increasing with age.(17)

Historically, Ph+ ALL has been one of the worst prognostic groups in pediatric ALL. In the largest study published to date, 326 children and adolescents less than 20 years old with Ph+ ALL diagnosed between 1986 and 1996 had a 7-year event-free survival (EFS) rate of 25% and overall survival (OS) rate of 36%.(15) In that study, matched related, but not unrelated donor stem cell transplantation (SCT) produced better outcomes than chemotherapy alone. A subsequent retrospective review of over 600 Ph+ ALL patients treated by fourteen pediatric cooperative groups from 1995-2005 showed modest improvements in outcome with 7-year EFS of 31% and OS of 44%.(18) This study included only patients who did not receive any TKI therapy, and thus serves as a baseline for future studies. SCT, using either matched related or unrelated donors, was a superior treatment strategy to chemotherapy, but results were still poor even with SCT.

Imatinib in Ph+ ALL

As imatinib was developed, a variety of studies showed that it was also effective in Ph+ ALL, but responses of patients with advanced disease to single agent therapy were typically very short-lived. Promising early results have been seen when imatinib was combined with chemotherapy in adults with Ph+ ALL, but the treatment strategies pursued typically focused on the use of SCT for consolidation therapy.(19, 20) The Children’s Oncology Group (COG) AALL0031 trial (2002-2006) incorporated imatinib, starting after completion of induction therapy, into a very intensive chemotherapy regimen in a stepwise fashion, with SCT reserved, per study criteria, for those patients with a matched related donor.(21) Patients in the last cohort of AALL0031 (#5) received continuous treatment with imatinib 340 mg/m²/day from the start of Consolidation, with the drug administered on a two week on/two week off schedule for the last year of maintenance therapy. The regimen was well tolerated, and there were no significant increased toxicities due to imatinib. Patients treated in cohort 5 had a 3-year EFS of 80%, which was more than double the EFS rate (35±4%; p <0.0001) of historical controls treated in the pre-imatinib era. There was no advantage for SCT with 3-year EFS similar for patients in Cohort 5 treated with chemotherapy plus imatinib, related donor SCT, or off protocol therapy unrelated donor SCT. While these results are based on relatively small patient numbers, they have been stable with longer follow-up, and suggest that addition of imatinib to intensive chemotherapy can dramatically improve the outcome of children with Ph+ ALL, and thus call
for a reassessment of routine use of SCT in this disease. However, there were several potential disadvantages to the AALL0031 treatment strategy. First, imatinib treatment was not started until induction therapy was concluded. Consistent with historical data, (15, 18) about 10% of patients failed to enter remission after 4 weeks of chemotherapy. Second, the chemotherapy regimen administered intensive treatment for a prolonged time with high cumulative doses of many agents. It is not clear whether or not the intensive chemotherapy contributed to the observed improvements in outcome, or whether similar outcomes could be obtained with more standard chemotherapy regimens plus a TKI.

In parallel to COG AALL0031, the major European pediatric cooperative groups have conducted the EsPhALL study for children with Ph+ ALL. This study took a different approach and originally randomized low risk Ph+ ALL patients to receive chemotherapy +/- imatinib, with higher risk patients non-randomly assigned to the + imatinib arm. By design, the rates of SCT are much higher on the EsPhALL study than in COG AALL0031 and dose intensity of imatinib is lower. The EsPhALL trial has recently been amended to use imatinib in all patients with earlier, and more intensive use of this agent.

Unanswered questions and future directions

There are several important unanswered questions in pediatric Ph+ ALL, including: (1) What is the optimal TKI to combine with chemotherapy?; (2) How intensive a chemotherapy backbone is needed?; and (3) What is the role of SCT in Ph+ ALL?

The COG is currently conducting AALL0622 as a successor to AALL0031. The AALL0622 chemotherapy backbone is identical to that used in AALL0031 with minor exceptions. Several observations led the COG to conclude that that optimizing TKI therapy was the best way to improve outcomes in Ph+ ALL. These included the very promising results of AALL0031 and results of a GMALL study in elderly adults with Ph+ ALL. (22) In that study, adults older than 55 years of age received a 5-day chemotherapy prophase (dexamethasone 10 mg/m²/day x 5 days, cyclophosphamide 200 mg/m² x 3, and one dose of intrathecal methotrexate) and then were randomized to receive a 4-week cycle of imatinib (600 mg/day) or a multiagent chemotherapy regimen. Following this, patients received chemotherapy + imatinib. The complete remission (CR) rate was much higher on the imatinib monotherapy arm (96% vs. 50%, p=0.0001) The COG also felt that available data suggested that dasatinib might be a more effective agent than imatinib for treatment of Ph+ ALL. In particular, in murine models signalling through SRC family kinases HCK, LYN, and FGR is required for development of Ph+ ALL, but not CML. (23) As noted above, dasatinib is a dual SRC/ABL TKI that is 325-times more potent than imatinib against BCR-ABL1 in vitro, and has activity against most imatinib-resistant BCR-ABL1 mutants. Finally, unlike imatinib, dasatinib crosses the blood-brain barrier and is effective treatment for central nervous system leukaemia in patients with Ph+ ALL. (24) Based on these data, AALL0622 uses dasatinib rather than imatinib, and also starts dasatinib therapy at day 15 of Induction. This timepoint was selected as it was felt to be the earliest time that was feasible for a large study that involves more than 100 centers.

AALL0622 was designed before the results of AALL0031 were available and includes options for matched related donor SCT for all patients, and matched unrelated donor SCT for patients with a poor early response to therapy, defined as minimal residual disease levels (measured by flow cytometry) of >1% at end induction or >0.01% at end of 2 months of consolidation therapy.

Future studies in Ph+ ALL will continue to focus on defining the optimal chemotherapy backbone, the optimal TKI, and the role of SCT in CR1. It will also be critical to develop new strategies for treatment of patients that have BCR-ABL1 point mutations that are resistant to the currently available 1st and 2nd generation TKIs. The most resistant point mutation in CML is T315I, which also occurs in Ph+ ALL. A number of agents, including Aurora kinase inhibitors, have been developed that can inhibit this and other highly resistant BCR-ABL1 mutations. (25, 26) One can anticipate that such agents might be combined with chemotherapy and a TKI to treat Ph+ ALL in the future.
Summary
The treatment of Ph+ leukemias is a paradigm for how molecularly targeted therapies can improve outcomes in human cancer. Because Ph+ ALL is a more “virulent” disease than CML (with more accumulated genetic lesions), TKI monotherapy is ineffective. However, combination regimens of chemotherapy + TKIs hold great promise for treatment of this disease. There are major questions remaining about how Ph+ pediatric ALL should be treated optimally. We can only hope that the next decade will be as productive as the past one has been in improving outcome for this once very recalcitrant subtype of leukemia.

References


