Treatment of Philadelphia positive (Ph+) ALL and CML in children

Andrea Biondi

Introduction
Philadelphia positive (Ph+) leukemias in children include essentially all chronic myeloid leukemias (CML) and 2% to 3% of childhood acute lymphoblastic leukemias (ALLs). Ph+ leukemias are characterized by a reciprocal translocation between chromosomes 9 and 22 (Philadelphia chromosome). The translocation creates a fusion of human homologue of the Abelson Murine leukemia virus ABL on chromosome 9q34, with breakpoint cluster region BCR on 22q11 (reviewed in ref. 1) An in frame BCR-ABL fusion transcript results in the upregulation of the abl tyrosine kinase. Primarily, three main BCR-ABL chimeric transcripts arise from distinct breakpoints in the BCR gene, resulting in fusion of the BCR exon 1, exon 1-12/13 or exons 1-19 to ABL. The molecular masses of the protein products are 185/190, 210 and 230 kDa respectively. In most patients with CML and in approximately 10% of patients of ALL it is the p210BCR-ABL product which is produced, although low levels of the p185BCR-ABL product are often detect in CML patients. For the majority of Ph+ALL and in occasional patients with CML, a p185BCR-ABL product is found. The alternative translocation product, ABL-BCR can be detected but is not thought to play a role in leukemogenesis (1).

The bcr-abl fusion proteins are characterized by a constitutive protein tyrosine kinase (PTK) activity that is absent in the normal abl protein. This dysregulated PTK activity, which results in changes of multiple signal transduction pathways, is crucial to the transforming activity of the bcr-abl fusion proteins and their ability to cause leukemias in vivo (1). Therefore, inhibition of the PTK activity of this oncprotein is a rational therapeutic approach for BCR-ABL expressing leukemia.

Imatinib is an inhibitor of the protein-tyrosine kinases associated with bcr-abl, the platelet-derived growth factor (PDGF) receptor and c-Kit, but not of other members of the Type III receptor kinase family, such as Flt-3 and Fms (2-3). Imatinib shows selectivity for the Abl protein-tyrosine kinase at the in vitro, cellular and in vivo levels. The compound specifically inhibits proliferation of bcr-abl expressing cells. In colony forming assays using ex vivo peripheral blood and bone marrow samples, Imatinib shows selective inhibition of bcr-abl positive colonies from CML patients. In animal models, the compound shows potent anti-tumor activity against bcr-abl and v-abl expressing cells at tolerated doses. Imatinib has dramatically changed the treatment of adult Ph+ CML (1-3) and showed promising results in adult Ph+ ALL in combination with chemotherapy (4).

Ph+ Acute lymphoblastic leukaemia (ALL)
Recent advances in treatment have increased the cure of childhood ALL to 75 percent or better (5,6). However attempts to improve results for resistant subtypes of ALL, such as Ph+ ALL, have been largely unsuccessful. Overall Ph+ALL, which accounts only for 2-3% of children with ALL have a dire prognosis (rates of EFS are 25-30% in children and even less in adults) (7). Some investigators suggest that Ph+ALL in childhood is heterogeneous with regard to sensitivity to treatment. Good initial response to steroids (which are given in combination with intrathecal methotrexate before induction chemotherapy is instituted) as well as age and leukocyte count at diagnosis, have been shown to correlate with a good clinical outcome in children treated only with chemotherapy (7-8). The heterogeneity of Ph+ALL with respect to clinical outcome has been recently confirmed by the analysis of the largest series of pediatric ALL treated by 10 European and United States study groups or large single institutions from 1986 to
Among patients who presented with WBC higher than 100 x 10^9/l, 85% did not have long-term EFS at five years. The inadequacy of current therapy for such patients, most of whom can be readily identified by their initial response to prednisone, indicates a need for new treatments. Patients who are younger than 10 years old and have a WBC less than 50 x 10^9/l at the time of diagnosis have about a 50 percent chance of long term DFS whereas the remaining patients (those with WBC of 50 x 10^9/l to 100 x 10^9/l and those with less than 50 x 10^9/l leukocytes who are older than 10 years of age) have an intermediate prognosis (estimate of five-year DFS, 30%) (7).

The prognostic impact of early response to induction was recently reported by the UK Medical Research Council ALL trial for childhood ALL, MRC ALL97 (10). Between January 1997 and June 2002, forty-two (2-3%) patients were Ph+. Nineteen (45%) had <25% blasts in bone marrow (BM) within the first 2 weeks of treatment and were defined as a good response group (GRG), the others as a poor response group (PRG). Thirty-six (86%) achieved first complete remission (CR1) at the end of induction, of which 28 underwent BM transplantation (BMT). The median follow-up was 42 months (range, 21–84). The 3-year event-free survival (EFS; 52%, 95% CI, 36–66%) was a considerable improvement on the previous MRC UKALL XI trial (27%). EFS for the GRG and PRG were 68% (43–84%) and 39% (18–59%), respectively (P = 0.03); presenting white cell count <50x10^9/L (P = 0.02) was predictive for overall survival.

Stem cell transplantation from HLA-matched related donor yields a significant better outcome than chemotherapy alone (7,11). The absence of any significant superiority to chemotherapy in patients undergoing SCT from a mismatched donor or matched unrelated donor (MUD), could be explained by the high number of transplantation-related deaths, reported in this study (11). In most recent years better results have been obtained with unrelated donor HSCT, in series which include either children and adults (12). The leukemic cell burden present before HSCT influences the rate of relapse-free survival: patients with detectable BCR-ABL-expression prior to HSCT have a significantly worse prognosis.

Scanty are the information on efficacy of Imatinib in pediatric Ph+ ALL, but according to the data obtained so far in adult patients with acute Ph+ leukemia or blast crisis of CML, the drug produce only a transient effect when used alone (4 and reviewed in ref.13). Accordingly, most ongoing trials in acute Ph+ leukemia, are exploring the possibility to incorporate Imatinib in the context of multi-agent approach (either in combination or during the interval of chemotherapy blocks). One group used a hyper-CVAD (fractionated cyclophosphamide, vincristine, Adriamycin and dexamethasone)-type regimen (14) and incorporated imatinib postinduction. They achieved a CR rate of 80% (15). Although approximately 50% of their refractory patients ultimately achieved CR when Imatinib was used postinduction, this is not significantly different from previous results without Imatinib. Two groups have used a similar hyper-CVAD regimen, but with the concurrent use of Imatinib during remission induction (16,17). All patients in these two studies were in CR at the end of induction and a high rate of molecular CR was achieved prior to allo-SCT. All three groups reported a high success rate post-allo-SCT when compared with historical controls and, reassuringly, the use of Imatinib does not appear to increase transplant-related morbidity.

Two cooperative studies are currently ongoing to test the relevance of Imatinib incorporation on intensive chemotherapy backbone for treatment of childhood Ph+ ALL. In the AALL0031, from the Children's Oncology Group (COG), the protocol chemotherapy is based on various promising components previously studied in other ALL COG trials. This includes the use of ifosfamide and etoposide from POG ALL relapse studies, the successful use of high dose methotrexate for ALL, and the CCG NY II regimen used in high risk ALL. Imatinib was planned to be gradually introduce in cohorts of patients in this study, with later cohorts receiving it in more phases of therapy if earlier cohorts are treated successfully without toxicity problems. Also, the subset of patients in this study who have an appropriate donor was eligible to receive hematopoietic stem cell transplant (HSCT) following the initial two courses of consolidation therapy in the study. The study was opened to patient entry on October 14, 2002 and based on
most recent accrual data, the study should reach its Ph+ target accrual goal by approximately May 2006 (Kirk Schultz, personal communication, January, 2006). All patients in the current European collaborative trial for Ph+ ALL in childhood (EsPhALL) are receiving remission-induction therapy as per national study group recommendations for children with ALL. Postinduction, all treatment will be on a common European collaborative protocol. All good responders are randomised to receive or not receive imatinib in addition to standard chemotherapy. For those receiving a prednisolone prophase, a good-responder is defined as one with a peripheral blast count of <1x10⁹/l at the end of a week. For children on other protocols, this is defined as blast count of <25% in a bone marrow aspiration taken during the first 2 weeks of induction. All other children are defined as poor-responders and receive Imatinib along with standard chemotherapy. The study was opened in 2004 and it will be completed in 2007.

**Chronic myelogeneous leukaemia**

Diagnosis of CML is rare in childhood; it accounts for only 3% of leukemias below the age of 18 yrs. Thus, data describing diagnostic features and the natural history of the disease are mostly depicted from small series of cases (18,19). In children the course of the disease seems not to differ from adult patients. However, the younger age generally qualifies pediatric patients as candidates for hematopoietic stem cell transplantation. Although treatments such as hydroxyurea and interferon alpha (IFNa), with or without cytarabine, may induce responses, they are not curative (20).

Similar to adult CML, the only potentially curative therapy for childhood Ph+ leukemias remains allogeneic stem cell transplantation, which is most effective with a matched sibling donor during the chronic phase of CML (21-25). Unfortunately, high rates of transplant-related mortality (approximately 20%) and posttransplantation recurrence (17%) may occur (21).

The substantial antileukemic activity of Imatinib in adult CML trials prompted investigators in the COG to evaluate this agent in children with recurrent or refractory Ph+ leukemias. The objectives of this phase 1 study were to determine the optimal dose of Imatinib for phase 2/3 pediatric trials, to evaluate the toxicities and plasma pharmacokinetics of Imatinib in children, and to provide a preliminary evaluation of the antileukemic activity of Imatinib in Ph+ childhood leukemias (26). The purpose of the study was to determine dose-limiting toxicities in children with refractory or recurrent Ph+ leukemias. Oral Imatinib was administered daily at dose levels ranging from 260 to 570 mg/m². There were 31 children who received 479 courses of Imatinib. The most common toxicities encountered, which occurred in less than 5% of courses, were grade 1 or 2 nausea, vomiting, fatigue, diarrhea, and reversible increases in serum transaminases. One patient at the 440-mg/m² dose level had dose-limiting weight gain. There were no other first-course dose-limiting toxicities. A maximum tolerated dosage was not defined. Among 12 CML patients evaluable for cytogenetic response, 10 had a complete response and 1 had a partial response. The Authors found that daily oral Imatinib is well tolerated in children at doses ranging from 260 to 570 mg/m². Doses of 260 and 340 mg/m² provide systemic exposures similar to those of adults who are treated with daily doses of 400 and 600 mg, respectively.

Although hematopoietic stem cell transplantation remains the treatment of choice for children with Ph leukemias whose physiologic state permits intensive therapy and for whom donors are available, Imatinib mesylate is an important option for facilitating induction of complete remission in children with recurrent or refractory disease or for whom there is not a suitable donor. On the basis of the results of our study and the favorable results obtained with newly diagnosed adult patients with CML (27), several cooperative pediatric study groups are currently evaluating the role of Imatinib in children with newly diagnosed Ph+ CML.

**References**


