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Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia in Childhood

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In pediatric patients with acute lymphoblastic leukemia (ALL), the Philadelphia chromosome translocation is uncommon, with a frequency of less than 5%. However, it is classified as a high or very high risk, and only 20–30% of Philadelphia chromosome-positive (Ph+) children with ALL are cured with chemotherapy alone. Allogeneic hematopoietic stem cell transplantation from a closely matched donor cures 60% of patients in first complete remission. Recent data suggest that chemotherapy plus tyrosine kinase inhibitors (TKIs) may be the initial treatment of choice for Ph+ ALL in children. However, longer observation is required to determine whether long-term outcome with intensive imatinib and chemotherapy is indeed equivalent to that with allogeneic related or alternative donor hematopoietic stem cell transplantation (HSCT). Reports on the use of second-generation TKIs in children with Ph+ ALL are limited. A few case reports have indicated the feasibility and clinical benefit of using dasatinib as salvage therapy enabling HSCT. However, more extensive data from clinical trials are needed to determine whether the administration of second-generation TKIs in children is comparable to that in adults. Because Ph+ ALL is rare in children, the question of whether HSCT could be a dispensable part of their therapy may not be answered for some time. An international multicenter study is needed to answer the question of whether imatinib plus chemotherapy could replace sibling allogeneic HSCT in children with Ph+ ALL.

Key words: Philadelphia chromosome, Acute lymphoblastic leukemia, Tyrosine kinase inhibitor, Child

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Introduction

Age is one of the most important prognostic factors in patients with acute lymphoblastic leukemia (ALL). In children, long-term survival rates are approximately 80%, but the rate decreases to less than 30% in adults[1]. Differences in survival may be attributable in part to age-dependent increases in unfavorable cytogenetic abnormalities. Until recently, Philadelphia chromosome-positive (Ph+) ALL children and adolescents were considered one of the poorest-risk subgroups of ALL patients. With chemotherapy alone, only 20–30% of

children with Ph+ ALL are cured. Allogeneic hematopoietic stem cell transplantation (HSCT) with a closely matched donor in first complete remission cures 60% of patients. The Philadelphia (Ph) chromosome is the most common cytogenetic abnormality in adult ALL, comprising 20–30% of adult cases; however, it occurs in only 3–5% of pediatric cases[2]. The Ph chromosome results from a reciprocal translocation between chromosomes 9 and 22 (t[9,22][q34;q11]), which produces a fusion gene on chromosome 22, namely, the breakpoint cluster region-Abelson leukemia viral proto-oncogene (*BCR-ABL*). *BCR-ABL* fusion proteins are constitutively active tyrosine kinases that can alter multiple signaling pathways, which contribute to tumor growth and proliferation. The molecular weight of this protein depends on the precise chromosome breakpoint. Most patients with ALL express a 190-kDa protein (p190), whereas the others express a 210-kDa oncoprotein (p210), which is also commonly found in chronic myeloid leukemia (CML)[3].

The role of allogeneic hematopoietic stem cell transplantation as a first-line therapy for Ph+ ALL

Although complete remissions (CRs) may occur in 70–90% of patients with Ph+ ALL who receive intensive chemotherapy alone, most patients relapse and die within 12 months of treatment[4]. Allogeneic HSCT substantially improves long-term survival rates, and in a large-scale trial, the 5-year relapse-free survival rate in the pre-imatinib era was 57% in patients who underwent a sibling allogeneic HSCT, 66% in patients who underwent a matched unrelated donor allogeneic HSCT, and 44% in patients who underwent an autologous HSCT, but the survival rate in patients who received chemotherapy alone was 10%. Although the allogeneic HSCT group fared worse initially because of high rates of transplantation-related mortality, the lower relapse risk translated to a higher 5-year event-free survival rate (EFS) (41% for sibling donor and 36% for matched unrelated donor) and a higher 5-year overall survival rate (OS) (44% for sibling donor and 36% for matched unrelated donor) compared with chemotherapy alone (EFS, 9%; OS, 10%) and autologous HSCT (EFS and OS, 29%)[5]. Several factors influence the outcome of patients who undergo allogeneic HSCT. Patients who underwent allogeneic HSCT in first CR had substantially better outcomes than those who underwent allogeneic HSCT during second or later CR. Other favorable factors include younger age, total body irradiation conditioning, the use of a human leukocyte antigen-identical sibling donor, and the occurrence of acute graft-versus-host disease.

Table 1. Key Points about Ph+ ALL in Children

Uncommon among pediatric ALL patients, with a frequency of less than 5%
The most common cytogenetic abnormalities in adult ALL, comprising 20 to 30% of adults
Classified as high or very high risk
With chemotherapy alone, only 20–30% of children with Ph+ ALL are cured.
Allogeneic hematopoietic stem cell transplantation in first complete remission cures 60% of patients with a closely matched donor.
Recent data suggests that chemotherapy plus TKIs may be the initial treatment of choice for Ph+ ALL in children.
Second-generation TKIs are more potent inhibitors of the BCR-ABL kinase when compared with imatinib. Only dasatinib and nilotinib are currently being evaluated as therapies for Ph+ ALL.
Side effects of TKI including gastric upset, cytopenias, peripheral edema, liver toxicity, pleural effusion, growth retardation, and possible premature closure of the growth plates resulting in short stature.
When TKI is added to therapy, higher complete remission rate without additional toxicity allows more patients to undergo allogeneic HSCT survival advantage

Recently, an Italian group analyzed treatment results according to time period. In a previous analysis of 326 children with Ph+ ALL treated between 1986 and 1996, compared with chemotherapy alone, HSCT with matched related donors yielded a superior outcome; however, this advantage did not extend to HSCT with matched unrelated donors[6]. To evaluate the impact of recent improvements in chemotherapy and transplantation, a similar analysis was performed on patients treated in the following decade[7]. In this study, the advantage of transplantation on disease-free survival (DFS) appeared during the second year of follow up and became significantly more evident with each successive year, which suggests greater protection against late relapse with HSCT (P<0.001). According to the Cox model, the hazard of failure (relapse or death in remission) at 5 years was reduced by two-thirds by HSCT than with chemotherapy alone (hazard ratio [HR], 0.32; 95% CI, 0.20–0.52). According to univariate comparison of the DFS curves at the 5-year time point, the advantage of transplantation was borderline significant (P=0.049). However, although the improvements in outcome achieved during the time period from 1996 to 2005 were statistically significant, only a small (10%) effect was observed on OS. Treatment with either chemotherapy or HSCT during this time period without tyrosine kinase inhibitor (at least during the front-line treatment program) resulted in long-term survival rates of less than 50% for all groups analyzed. Overall, only 45% of children with Ph+ ALL were alive 7 years after diagnosis, a result that remains unacceptable, and further optimization of the chemotherapy or HSCT regimen is unlikely to lead to major improvements in outcome[7].

Imatinib, a major advance in the treatment of Ph+ ALL

Imatinib mesylate, the first BCR-ABL inhibitor to gain clinical

approval, partially blocks the adenosine triphosphate (ATP) binding site of BCR-ABL, thus preventing the conformational switch of the oncogenic protein to the activated form[8]. Early trials of imatinib were performed in adults with Ph+ ALL or CML in lymphoid or myeloid blast crisis. Imatinib doses ranged from 300 to 600 mg/day, and 73% of evaluable patients had a 50% or greater reduction in marrow or peripheral blasts after 4 weeks of therapy. Toxicity was minimal, but a possible effect on platelet function leading to an increased bleeding tendency was identified[9].

Data for children lagged behind that for adults. In a Children's Oncology Group (COG) Phase I trial, imatinib was increased from 260 to 570 mg/m^2/day in 31 children. Toxicities were minimal, occurring in less than 5% of courses, and were primarily grade 1 or 2 nausea, vomiting, fatigue, diarrhea, and reversible increases in serum transaminases. No maximum tolerated dosage was defined. Doses of 260 and 340 mg/m^2 provided systemic exposures similar to those of adults who were treated with daily doses of 400 and 600 mg, respectively[10]. On the basis of these findings, Phase II/III trials were developed to evaluate the role of chemotherapy plus imatinib in childhood Ph+ ALL. The 3-year EFS was 88±11% for chemotherapy plus imatinib, which is more than twice that of historical controls (35±4%; P<0.0001). The results were comparable to those of patients biologically assigned to treatment with human leukocyte antigen (HLA)-identical sibling stem cell transplantation (SCT) (57±22%) and those of patients treated with unrelated donor SCT (71.6±19.0%)[11]. This suggests that chemotherapy plus tyrosine kinase inhibitors (TKIs) may be the initial treatment of choice for Ph+ ALL in children. However, the numbers in this trial are small and the historical controls included children treated over a long period in the past. Furthermore, the comparative survival curves highlighted the very short follow up for the study cohort. This is particularly relevant since earlier studies examining the outcome of Ph+ ALL demonstrated the occurrence of late relapses in children treated with chemotherapy alone, whereas relapses following allogeneic HSCT typically occurred early or were absent. In summary, the cumulative evidence indicates that imatinib is an extremely valuable addition to induction therapy for Ph+ ALL. Imatinib certainly increases the ability of therapy to generate complete remissions and very likely allows more patients to undergo allogeneic HSCT. However, it appears unlikely to represent a long-term curative option for patients with Ph+ ALL. The standard practice continues to be imatinib used in combination with chemotherapy from diagnosis in order to achieve a rapid response and facilitate early allogeneic HSCT, which is presently considered to offer the best anti-leukemic activity[12].

Second-generation TKIs

Several second-generation TKIs have been identified as potential therapies for Ph+ ALL. These include dasatinib, nilotinib, bosutinib, DCC-2036, AP24534, and AT9283[13]. All of these agents are more potent inhibitors of BCR-ABL kinase than imatinib, but only nilotinib and dasatinib are currently being evaluated as therapies for Ph+ ALL.

1. Dasatinib

Dasatinib, a dual *SRC* and *ABL* inhibitor, has 325-fold greater potency than imatinib in cells transduced with unmutated *BCR-ABL* and is active against many *BCR-ABL* mutations that confer imatinib resistance[14]. Although it is more toxic than imatinib, dasatinib is a more attractive Ph+ ALL therapy candidate than imatinib because of its broader spectrum of action. Furthermore, dasatinib has marked activity in relapsed or resistant Ph+ ALL, and another advantage of dasatinib is that, unlike imatinib, it has excellent central nervous system (CNS) penetration. In one report, dasatinib produced improvement in the cerebrospinal fluid in all 11 adult and pediatric patients with CNS Ph+ ALL, and the response was long-lasting in 7 patients[15]. Myelosuppression was common but not dose limiting, and tolerability in the context of combination chemotherapy was less clear. Dasatinib has been approved for use by the USA and Korea FDA for patients with Ph+ ALL who have failed to respond to imatinib, and clinical trials evaluating its efficacy in patients with newly diagnosed Ph+ ALL are ongoing. Currently, the COG is evaluating dasatinib in combination with the same intensive chemotherapy backbone as in the previous study with imatinib. The primary goals of this study are to assess the safety and feasibility of substituting dasatinib for imatinib in the previous COG chemotherapy backbone and to determine whether intensive chemotherapy plus dasatinib will result in a 3-year EFS of at least 60% in patients with Ph+ ALL[16]. Given the early superiority of dasatinib in CML, if dasatinib is well tolerated in the COG trial, a randomized comparison versus imatinib in Ph+ ALL will be considered.

2. Nilotinib

Nilotinib is a highly specific *BCR-ABL* inhibitor that is approximately 30-fold more potent than imatinib, and is active in vitro against 32 of 33 *BCR-ABL* mutants[17]. A phase I study of nilotinib in patients with imatinib-resistant CML and Ph+ ALL indicated that nilotinib had a relatively favorable safety profile, and responses were noted in a subset of adult patients with imatinib-resistant Ph+ ALL. In particular, 10% of patients who had hematologic relapses achieved a partial hematologic response, and 33% of patients with persistent

molecular signs of ALL achieved complete molecular remission after nilotinib therapy[18]. A subsequent phase II study of nilotinib (400 mg twice daily) in relapsed or refractory Ph+ ALL reported that 24% patients attained a complete hematologic response[19].

Side effects of TKI with chemotherapy

Imatinib has numerous short-term side effects including gastric upset, cytopenia, peripheral edema, and liver toxicity (reversible elevation of transaminases). Pleural effusion, which was not severe, has also been observed with dasatinib. The only major toxicity observed with imatinib in prepubertal children has been growth retardation and possible premature closure of the growth plates resulting in short stature[20, 21]. This has been observed with long-term imatinib usage in children with CML and may not be a major factor when used for only approximately 2.5 years as in the COG study. Other TKIs probably have the same effect on growth .

The impact of known risk factors in childhood ALL

Age, white blood count (WBC) at diagnosis, minimal residual disease (MRD), and complex cytogenetics are the well-known risk factors that affect outcome in children with ALL. In a retrospective analysis of patients treated without TKI, a high WBC count and age over 10 years suggested a poor prognosis with chemotherapy. However, in the recent COG trial, the differences were much lower and were not significantly different[11]. A slow prednisone response and higher MRD also suggested a poor prognosis in German trials and are being used for risk assignment in the current trial[22]. In the COG trial with longer follow up, MRD appears to be more prognostic, but is still not significant. Therefore, MRD is currently being used to determine high-risk patients in the COG dasatinib plus chemotherapy trial. Complex cytogenetics has also been shown to be a poor prognostic factor in adult Ph+ ALL[23]. However, in the COG trial, complex cytogenetics did not predict outcome[24].

Conclusion and future directions

Ph+ ALL children and adolescents were once the poorest-risk subgroups of ALL patients. With chemotherapy alone, only 20–30% of children with Ph+ ALL are cured. Allogeneic HSCT from a closely matched donor in first complete remission cures 60% of patients. Although TKIs have limited activity against Ph+ ALL as a single agent, they have been evaluated in combination with chemotherapy and have shown promise. Early results of the COG trial have shown an 88% 3-year EFS for Ph+ patients treated with intensive chemotherapy plus continuous imatinib. This suggests that chemotherapy plus TKIs may be the initial treatment of choice for children with Ph+ ALL. However, in this trial, the numbers are small and confirmatory results are not yet available. It is possible that the major benefit of using TKI will be accompanying transplant; first, to allow a greater proportion of patients to receive allogeneic HSCT, and second, to provide a sufficient level of post-transplant disease suppression to allow time for a graft-versus-leukemia effect to eliminate residual ALL in those who undergo transplantation with persistent MRD that is not eradicated by the conditioning therapy. The first patient group in whom omission of transplant is likely to be tested will be in children, because in younger patients there is a better outcome with chemotherapy alone, and younger individuals have more to lose by risking the long-term adverse consequences of allogeneic HSCT. However, because Ph+ ALL is rare in children, the question of whether HSCT can be a dispensable part of their therapy may not be answered for some time. An international multicenter study is needed to answer the question of whether imatinib plus chemotherapy could replace sibling allogeneic HSCT in children with Ph+ ALL. Key points about Ph+ ALL in children are summarized in Table 1.

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