Controversies in the Treatment of CML in Children and Adolescents: TKIs versus BMT?

Meinolf Suttorp, Isaac Yaniv, Kirk R. Schultz

Chronic myeloid leukemia (CML) is a relatively rare hematopoietic malignancy in the pediatric and adolescent population. This makes it difficult to perform clinical trials that can define the best therapeutic option when considering the impact of tyrosine kinase inhibitors (TKIs) versus the established approach of allogeneic hematopoietic cell transplantation (HCT). With the relatively low toxicity of TKIs, there are little data regarding when HCT or long-term TKI therapy is a better option. There are even less data regarding the duration of TKI treatment in the pediatric CML in chronic phase (CML-CP) patients who may receive over 60 years of therapy. As children and adolescent are treated for longer times with TKIs, it has become clear that toxicities may make long-term TKI therapy less attractive compared to allogeneic HCT. HCT has the long-term complications of growth failure, infertility, chronic graft-versus-host disease (GVHD), metabolic syndrome, and secondary malignancies, whereas prolonged TKIs may cause growth failure, hepatic, and cardiac complications. Moreover, HCT is a potentially curative intervention, whereas TKI is not curative, requiring prolonged exposure. In this article, we discuss the relative merits of the two therapeutic approaches and recommend that all children and adolescents with CML-CP should initially be treated with imatinib and maintained with TKI therapy indefinitely if there is a good response. We recommend that allogeneic HCT with an HLA-identical sibling donor or closely matched unrelated donor be considered for patients with treatment failure or recurrence after receiving salvage second-generation TKI treatment. We also conclude that randomized international trials are urgently needed to evaluate the best therapies for pediatric CML.

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INTRODUCTION

Chronic myeloid leukemia (CML) is a rare hematopoietic malignancy representing only 3% of pediatric and adolescent leukemias [1,2] and 2% of all CMLs. Because only 110 to 120 pediatric and adolescent CML cases are seen each year in the United States and Canada and a slightly higher number in Europe, it is difficult to perform clinical trials that can define the best therapeutic option when considering the impact of tyrosine kinase inhibitors (TKIs) versus the established approach of allogeneic hematopoietic cell transplantation (HCT). As TKIs appear to have a relatively low toxicity profile, it is attractive to consider this a better option for all situations compared to allogeneic HCT. However, there is little data to guide the pediatric oncologist regarding duration of TKIs in the young patient when it may mean over 60 years of TKI therapy for a young child affected with CML in chronic phase (CML-CP). As children and adolescent are treated for longer times with TKIs, it has become clear that TKI-related toxicities may make long-term TKI therapy less attractive compared to allogeneic HCT, and that TKIs are not curative, allowing their discontinuation at a particular time point. The following article will present the current data and controversies associated with TKI versus allogeneic HCT as therapy for children and adolescents with CML, and hopefully will help the pediatric oncologist make good decisions regarding their patients with CML.
THE CASE FOR PROLONGED TKI THERAPY FOR CHILDREN AND ADOLESCENTS WITH CML

Correlations between molecular effects of imatinib on BCR-ABL and clinical efficacy in CML have been well established. Today, imatinib has become the first-line therapy for all phases of CML in adults. Also, the appropriate management of children with CML has been changed radically as only a minority of pediatric patients are treated now by HCT upfront. Data from adults show that the effect of time between diagnosis of CML and HCT on overall survival (OS) may no longer be important under TKI treatment.

However, the issue of how long the treatment should be continued still remains unsolved. Prognostic factors applicable in adult CML to identify high-risk patients at diagnosis, like the Sokal and Hasford scores, are not established for children. Possibly, as in adults, the early response to imatinib is a relevant parameter for judging the aggressiveness of CML [3].

As an optimized therapeutic approach, close monitoring of treatment response (CHR: complete hematologic response; CCyR: complete cytogenetic response; MMolR: major molecular response), short- and long-term side effects, and prognostic factors is required. In addition, the treatment benefits of second-line therapies (HCT, second-generation TKI) must be considered.

Evidence from Pediatric Trials on CML

Because of the low incidence of CML in children, only a few pediatric studies have evaluated efficacy of treating this disease with TKI therapy in children and adolescents. A Children’s Oncology Group phase I study evaluated 20 patients with CML after interferon failure and imatinib-induced CHR in all children in CML-CP and CCyR in 83%. Responses were also seen in more advanced phases but were not persistent [4]. Thirty children were enrolled in a phase II trial in Europe. Entry criteria were advanced phase disease, relapse after HCT, or failure of interferon. In those children with CML-CP, imatinib induced a CHR in 80% and a cytogenetic remission in 12 of 20 CML-CP and in 2 of 7 CML-AP. No patient in CML-AP or CML-BC attained a molecular remission, but 6 of 8 had a CHR [5]. Forty-four children with de novo CML-CP were enrolled in a French phase IV study. After a median treatment duration of 16 months, the CHR rate was 86% and 98% at 3 months and 6 months, respectively, whereas 62% of patients achieve CCyR at 12 months. The proportion of MMolR was 34% at 12 months [6]. Fifty-one patients have been enrolled in the ongoing German Berlin-Frankfort-Muenster (BFM) phase IV trial. Comparable to results observed in the adult patients entering in CML-CP showed that 40 of 42 patients (95%) had achieved CHR at month 3; 26 of 28 (93%) were CCyR at month 12, and 17 of 19 (85%) were MMolR at month 18 after starting imatinib [7]. Taken together, pediatric patients in CML-CP appear to respond to TKI therapy as well as adults. Whether or not the kinetics of the response rates differ in younger patients remains to be determined.

Dose of Imatinib

Doses of 260 to 340 mg/m² imatinib in children give drug exposures similar to the 400-mg dosage recommended in adults. Therefore, children should receive 300 mg/m² orally once daily (maximum absolute dose 400 mg) [4]. In adults, doses of imatinib higher than the standard 400 mg/day result in more rapid attainment of molecular response but do not result in better progression-free survival (PFS) rates [7]. The recommended pediatric doses for CML-AP are 400 mg/m² daily (maximum absolute dose 600 mg) and for CML-BP 500 mg/m² daily (maximum absolute dose: 800 mg) [8].

Short- and Long-Term Toxicity of Tyrosine Kinase Inhibitors

Imatinib short-term toxicity is common, but the effects are generally mild to moderate and are very manageable. Children primarily have gastrointestinal tract toxicity [4,8], and imatinib should be taken with meals dissolved in apple juice (more soluble at low pH) to minimize nausea. Other common side effects include diarrhea, skin rash, edema, a mild transaminitis early in the course of treatment, and cytopenias. Some patients may experience lethargy and weight gain. Myalgias/cramps, usually mild to moderate, occur more frequently at night or with exertion. Bone pain, may occur in up to 10% of children and tends to fade with longer therapy. Female teenagers should avoid conception while taking imatinib, because of a risk for fetal abnormalities [9]. Studies in vitro and in animals suggest that imatinib inhibition of ABL in cardiac tissue may cause cardiac toxicity. Large adult studies found that cardiac toxicity is very rare; however, this might be a potential concern for long-term therapy in children.

Studies in adults have suggested that hypophosphatemia and dysregulated bone remodeling may be a side effect of TKI treatment (for review, see [11]). Supporting these clinical data, chronic exposure to imatinib causes the femoral length of juvenile mice to be reduced with premature growth plate closure in adult rats [12,13]. In prepubertal children, single case reports have demonstrated significant longitudinal growth retardation [10,14,15]. In a French trial, 30 children exhibited a highly significant (P < .0001) decrease of body height Z-score with a median of −0.37 over the first year of imatinib treatment [6]. A prospective analysis of 57 children treated with imatinib in the German trial demonstrated hyperparathyroidism in 25% of the cohort, a significant decline in bone resorption markers in 60%, and elevated osteocalcin levels (marker of bone
formation) at the beginning of imatinib therapy, which subsequently declined during further treatment before reaching a normal range [16]. Prepubertal patients appear to be affected more severely, and careful monitoring of longitudinal height as well as bone metabolic markers should be mandatory under imatinib treatment. The optimal approach to treat children suffering from this side effect is still undefined. Second-generation TKIs like dasatinib and nilotinib are expected to have the same potential for skeletal effects [11].

Definition of Response and Failure

During treatment, the development of imatinib resistance, intolerance, noncompliance, or progression to advanced-phase disease must be identified in a timely fashion. With no established specific recommendations for children, it appears to be advisable to follow the guidelines for monitoring residual disease in adults as proposed by the European LeukemiaNet (http://www.leukemia-net.org) [17]. Examination of blood count and differential and normalization of spleen and liver size should indicate hematologic response earlier than 3 months from the onset of treatment. CCyR, as indicated by Philadelphia-chromosome negative marrow cell metaphase, should be achieved after 12 months of treatment. Concerning quantitative RT-PCR assessment of BCR-ABL transcript levels to determine the molecular response, it must be stressed that the sensitivity level for detection of low numbers of transcripts varies among laboratories. The established International Scale and the development of reference reagents for testing laboratories to derive conversion factors to that scale have provided significant advances toward the standardization of quantitative RT-PCR for BCR-ABL. A rate of ≤0.1% is considered as MMolR and should be achieved within 18 months of treatment. Failure of imatinib primarily comprises resistance or drug intolerance. Resistance is categorized into primary resistance as a lack of efficacy from the beginning of treatment, or secondary (acquired) resistance defined as an initial response followed by a loss of efficacy with time (either molecular or cytogenetic). Resistance may be multifactorial, including BCR-ABL mutations of the kinase domain interfering with imatinib binding, BCR-ABL amplification or overexpression, clonal evolution, and decreased imatinib bioavailability or cell exposure. Patients who cannot continue taking imatinib because of adverse effects are regarded as intolerant. If imatinib failure is observed, second-generation TKI may be beneficial [9].

Second Generation Tyrosine Kinase Inhibitors in Pediatrics

In adults, about 50% of those who fail imatinib because of resistance and a slightly higher proportion of those who fail because of intolerance will benefit from switching to either dasatinib or nilotinib. Two randomized phase III studies demonstrated that dasatinib and nilotinib were superior as initial therapy to imatinib after 1 year of treatment [18,19]. In children, only limited data are available on second-generation TKIs for CML. Dasatinib was studied in a phase I and an ongoing phase II study in relapsed/refractory Ph+ leukemias resistant/intolerant to imatinib [20]. Among 41 evaluable patients on a dasatinib dosage of 60 to 80 mg/m²/day, a complete hematologic response (CHR) of 75% was seen in CML-CP, and a major cytogenetic response rate (MCyR) of 88% in CML-CP. Dasatinib was well tolerated up to a dose level of 120 mg/m², and treatment-related toxicities were mild to moderate in severity (more than grade 4) with nausea and diarrhea most frequent. So far, no pediatric data are available for nilotinib, and there is an urgent need for clinical trials similar to that in adults [21,22].

Monitoring and Steering of Therapy

Disease response should be carefully monitored with standardized RT-PCR in the long term [17]. Before a diagnosis of failure is made possible, adverse effects of drug interactions must always be excluded. Determination of blood drug level may be helpful to identify noncompliance to regular drug intake—a problem more frequently observed in teenagers experiencing side effects. Monitoring will identify cases of optimal response, which should continue imatinib as long as the treatment is effective, whereas in cases of failure to respond, second-generation TKIs and/or HCT should be considered [8]. A decision to change to either dasatinib or nilotinib should be based on the actual knowledge accumulated with these drugs in pediatric cohorts, and ideally these children are enrolled on clinical trials. Occasional patients may develop rapidly progressive disease. A 1 log-fold increase in the BCR-ABL/ABL transcript rate is highly suspicious of loss of response. In this situation, mutation analysis will help to decide whether it is helpful to increase the dose of imatinib or change to a second-generation TKI. It must be remembered that survival remains stage dependent and that both second-line TKIs dasatinib and nilotinib are ineffective against mutation T315I BCR-ABL. By this approach, it is possible to postpone HCT to a point of time before the disease progresses to hematologic relapse. Concerns that the use of imatinib prior to HCT might jeopardize OS seem to be unsubstantiated. However, a transplant in CML-AP is largely unsuccessful.

Can CML Be Cured if Tyrosine Kinase Inhibitors Are Discontinued?

Durable MMolR is observed in the majority of CML patients with imatinib treatment after 1 to 2 years. A new challenge for further optimizing the management of CML is to determine if treatment with
TKIs could eventually cure the patients, particularly those 5% to 10% children with sustained undetectable disease (F. Millot, M. Suttorp; unpublished observation). In adults, a pilot study was updated recently reporting on the first adult patients who discontinued imatinib for different reasons after having achieved a complete molecular response lasting >2 years. Half of the patients relapsed mostly within <6 months after discontinuation, but molecular remission could be regained by reinstitution of imatinib. With an impressively long follow-up interval of median 42 months after discontinuation, the authors confirmed that CMR can be sustained in the other half of the patients, particularly in males and in patients with CML with cytotoxic NK cells in their peripheral blood [23]. Efforts are presently undertaken by the CML Working Group of the I-BFM Consortium to initiate a collaborative “Stop imatinib” trial in which those few 5% to 10% of pediatric patients with sustained CMoR should be included. In addition, a trial in patients having achieved a sustained MMoR will test the efficacy of an interval treatment (1 month on/1 month off) aiming to minimize long-term side effects of TKI in not outgrown patients (personal communication: Eveline de Bont, Groningen, The Netherlands).

Transplantation in Children and Adolescents with CML: Open-Ended Versus Curative Therapy

More than 25 years ago, HCT provided proof of principle that CML could be cured by eradicating the malignant clone. To this day, an allogeneic HCT using marrow, peripheral blood stem cell, or cord blood donor sources remains the only known treatment available to cure patients with CML.

HCT Studies on Adult CML

In the last decade, TKI therapy has changed the role and frequency of HCT for CML in the adult population has been dramatically reduced [24]. According to data from the EBMT Chronic Leukemia Working Party, mortality following matched sibling donor transplant for CML in adults has decreased substantially. Patients in first CML-CP, with an EBMT risk score of 0-2, who received transplants from a matched sibling donor following a standard conditioning regimen between 2002 and 2005 (n = 214), had a transplant-related mortality (TRM) rate of 10%, with a 5-year relapse-free survival (RFS) of 61% [25]. The German study in adults reported a 91% 3-year survival for patients receiving transplants in CP, 90% of whom achieved a molecular CR with a TRM of only 8%. Survival was comparable to patients receiving imatinib [26]. Goldman et al. [27] recently reported on the long-term outcomes of a large cohort of CML patients in CP1 undergoing allogeneic HCT. OS rates at 15 years were 88% for sibling HCT and 87% for unrelated donor HCT. They concluded that recipients of allogeneic HCT for CML in first CP who remain in remission for at least 5 years have favorable subsequent long-term survival.

HCT Studies on Pediatric CML

Although the clinical course of CML in children seems to be similar to that of adult patients, children and adolescents are excellent candidates for HCT. The outcome of HCT in children with CML is similar to that of adults, with registry studies suggesting a long-term OS of approximately 70% [28]. The risk score developed by the European Group for Blood and Marrow Transplantation (EBMT) for adult patients may allow for a valid assessment of transplant risk in the pediatric population as well [29].

In a registry report from the EBMT, the OS at 3 years for children transplanted in first chronic phase (CP1) from sibling donors or unrelated donors was 75%, and 65%, respectively. However, TRM was high: 20% in transplants from matched siblings and 31% for recipients of unrelated donor transplants. Outcome for patients who received transplants in advanced stage was significantly worse [30].

The prospective CML-pediatric I trial, running from 1995 to 2004, aimed to transplant children with CML in first CP from an HLA-matched family donor within 6 months and from an unrelated donor within 12 months after diagnosis, after initial treatment with hydroxyurea ± interferon alpha (IFN-α) [31]. This approach resulted in an excellent 5-year event-free survival (EFS) of 87% ± 11% in the group grafted from HLA-identical family donors (n = 41). In contrast, those who were transplanted from an HLA-matched unrelated donor had a 5-year EFS of only 52% ± 9% (n = 71), and those who were grafted from an HLA-mismatched unrelated donor had a 5-year EFS of 45% ± 16% (n = 36). Those patients who were transplanted in first CP within 6 months from an HLA-fully matched donor (n = 144) had a 5-year EFS of 74% ± 9%. This trial was stopped because of poor patient accrual once imatinib had been fully licensed, as pediatricians recommend this new drug as initial treatment. Similarly, a French study reported OS and PFS of children transplanted in first chronic phase of 73% and 27%, respectively, for those who received transplants for advanced phase disease. TRM accounted for more than 90% of the deaths, and the single most frequent cause of death was GVHD [32].

Immune Mechanisms That Impact on the Efficacy of HCT

HCT is the treatment of choice for patients who have progressed beyond CP1. Transplantation is also recommended for patients with the T315I mutation, those who fail to achieve a CyR, or those in cytogenetic
relapse at 12 months from diagnosis. In accelerated phase and blast crisis, the use of any donor available should be considered [33]. A role for a natural killer (NK)-mediated anti-CML response after HLA identical sibling HCT through stimulatory KIRs present in the donor, has been recently demonstrated [34]. HCT following reduced-intensity conditioning (RIC) has been shown to be feasible in CML. However, only a few pediatric reports have been published to date [35-37]. RIC transplants should theoretically decrease early TRM and long-term conditioning-related side effects, by avoiding radiation and reducing chemotherapy doses.

Posttransplantation therapy for residual disease, including withdrawal of immune suppression, donor lymphocyte infusion (DLI), and the use of TKIs, are highly effective in CML [38,39]. Imatinib or a second-generation TKI should be used if the relapse occurs early after transplant, precluding aggressive immunotherapy use and/or if the child has active GVHD.

Transplant-Related Toxicity Compared to TKI Toxicity

The price for “cure” by TKI includes life-long medication and the consistent use of contraception, whereas the estimated long-term financial cost for the TKI treatment of an adolescent is US$1.9 million compared to about US$250,000 for allogeneic HCT. In countries with limited resources, the cost of a RIC transplant from a matched family donor is comparable to 180 days of TKI therapy and should be considered, especially for the pediatric age group [40,41].

Myeloablative HCT is not only associated with acute short-term toxicities but also long-term complications such as chronic GVHD (cGVHD), growth retardation, infertility, metabolic syndrome, organ toxicity, and second malignancies. RIC HCT is associated with reduced TRM, use of fewer blood products, reduced incidence of infection, and shorter hospitalization. However, reduction in long-term complications still remains to be proven.

A major concern regarding protracted TKI therapy is reduced compliance in adolescent patients due, in part, to side effects such as weight gain, abdominal cramps, diarrhea, and fatigue; these may lead to a higher incidence of disease recurrence than that observed in adults. Some studies suggest that TKI therapy is less effective in the general community than in clinical trials, a factor more relevant for the generally less-compliant adolescent population [42]. Compliance is an issue in post HCT management of adolescents, as well, especially those with cGVHD and could be similar to life-long TKI treatment.

The Role of TKIs in Transplantation

Lee et al. [43] have shown that treatment with imatinib prior to HCT, provided that patients remain in CP at the time of transplant may be associated with benefits. In a recent study from Japan, retrospectively reviewed the outcomes of unrelated donor HCT in 125 children with CML. The probabilities of 5-year OS and leukemia-free survival (LFS) were 59.3% and 55.5%, respectively. Of the 17 patients treated with imatinib, 15 (88%) achieved MCyR at the time of bone marrow transplant (BMT), and this group had an excellent 5-year OS of 81.9%. Transplants appears to be most effective in this setting of minimal residual disease (MRD), and TKI therapy may be most useful given before HCT [44]. The role of TKIs post-HCT except to treat disease progression is not known.

Imatinib, dasatinib, and nilotinib all may have immunosuppressive effects. Imatinib has efficacy in the treatment of cGVHD [21,22]. In murine models, dasatinib inhibits tumor necrosis factor alpha (TNF-α) and interleukin (IL)-6 production by macrophages after TLR4 stimulation by LPS [45]. This may explain the development of hemorrhagic colitis as a side effect in some patients treated with dasatinib [46]. Dasatinib can inhibit development of antigen specific CD8+ and CD4+ T cell responses potentially negatively affecting its efficacy [47]. In a phase II clinical study of 46 adults with Ph+ ALL, lymphocytosis secondary to dasatinib correlated with a superior survival. Thus, dasatinib may induce immune reactivity associated with good clinical responses.

International collaborative studies are needed to evaluate the role of HCT for pediatric CML in the TKI era. Recently, the IBFM HCT group has opened a study to reduce TRM (better HLA-typing, reduced conditioning), avoid late effects (infertility, cGVHD), and prevent hematologic relapse in children and adolescents with CML by using both improved posttransplant surveillance and posttransplant therapy including DLIs and TKIs for residual disease. Donors may be a matched sibling donor, or a 10 of 10, 9 of 10 unrelated adult donor, or unrelated cord blood. Monthly molecular monitoring is performed. Intervention for detected residual disease during the first year posttransplant uses or when GVHD is present is based on TKI therapy, whereas beyond 1 year with no GVHD, DLI is employed. This study will hopefully provide better evidence-based data to determine the best therapeutic options for children and adolescents with CML.

SUMMARY

In summary, the relative role of HCT versus prolonged TKIs is very uncertain in the pediatric and adolescent populations. The long-term effects of prolonged TKI usage appears to be lower than that seen with HCT, although only HCT can achieve a permanent remission. Any recommendation in children and adolescents is difficult to defend because of the
Table 1. Response Assessment, Warnings, Monitoring Intervals, and Interventions for CML Patients Treated with Imatinib and after SCT (see [16])

<table>
<thead>
<tr>
<th>Time Point*</th>
<th>Insufficient Imatinib Response</th>
<th>Imatinib Failure</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring During TKI Therapy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td>—</td>
<td>—</td>
<td>High-risk disease according to Sokal/Hasford risk score</td>
</tr>
<tr>
<td>At 3 months</td>
<td>Less than complete hematology response</td>
<td>No hematologic response (stable disease or disease progression)</td>
<td>Not first chronic phase Add. cytogenetic abnormalities in Ph+ cells (Del 9q+)</td>
</tr>
<tr>
<td>At 6 months</td>
<td>Less than partial cytogenetic response (Ph+ &gt;35%)</td>
<td>No cytogenetic response (Ph+ &gt;95%)</td>
<td>Any new cytogenetic abnormality in Ph+ or Ph− cells</td>
</tr>
<tr>
<td>At 12 months</td>
<td>No complete cytogenetic response (Ph+ &gt;95%)</td>
<td>No major cytogenetic response (Ph+ &gt;35%)</td>
<td>Any new cytogenetic abnormality in Ph+ or Ph− cells</td>
</tr>
<tr>
<td>At 18 months</td>
<td>Less than major molecular response (no 3 log reduction)</td>
<td>No complete cytogenetic response</td>
<td>Any new cytogenetic abnormality in Ph+ or Ph− cells</td>
</tr>
<tr>
<td>At any time</td>
<td>Loss of response</td>
<td>Disease progression</td>
<td>Any new cytogenetic abnormality in Ph+ or Ph− cells</td>
</tr>
</tbody>
</table>

**Intervention:** SCT might be considered, depending on EBMT risk score at time of warning, insufficient response, or failure.

**Monitoring** post-SCT:
- Analysis of bone marrow aspirates by real-time quantitative RT-PCR at +1, +2, +3, +6, +9, +12 months after SCT; increase the assay frequency as needed.
- **Definition of low-risk patient:**
  1. Reduction of BCR-ABL mRNA levels by at least 2 log from baseline at 1 month post-SCT and continuous decline thereafter following SCT.
  2. Achievement of MMoR (ratio abl/bcr-abl ≤0.1%) and maintenance of this stable BCR-ABL transcript level post-SCT or continuous decline thereafter following SCT.
  3. Development of aGVHD grade II-IV or extensive cGVHD and Ph+ chromosome negative and stable or decreasing BCR-ABL transcript levels after SCT.
  4. CMoR (RT-PCR negative) after SCT.
- **Intervention:** No intervention for low-risk patients.
- **Definition of high-risk patient:** Not qualifying for any criteria of the low-risk group.
- **Intervention:** Based on individual decisions including withdrawal of immunosuppression, escalating donor lymphocyte infusions, and imatinib mesylate.

*SCT indicates stem cell transplantation; GVHD, graft-versus-host disease.
*During the first 2 years, monitoring should occur every 3 months. If a major molecular response (≤0.1%) is achieved, the monitoring interval may be prolonged. However, there are no pediatric data in support of this practice, and until further pediatric data are available, we recommend that peripheral blood be monitored for BCR-ABL every 3 months indefinitely.
lack of available clinical data. Based on the adult data and what little is known in children, a reasonable approach appears to be initial treatment with imatinib in children and adolescents with CML-CP, with a change to a second-generation TKI if there is an incomplete response or recurrence after an initial response. At the time of a change to the second-generation TKI, an allogeneic HCT from either a matched sibling or closely matched unrelated donor should be implemented. Monitoring recommendations of BCR-ABL for CML on TKI therapy or after HCT can at this time only be extrapolated from adult data with the caveat that these populations should be more closely monitored until additional data are obtained (Table 1). The long-term effects of TKI usage lasting for a number of decades represent a very big unknown factor as pediatric oncologists consider the most appropriate treatment for their patients with CML. We also conclude that randomized international trials are urgently needed to evaluate the best therapies for pediatric CML.

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REFERENCES


