Pediatric chronic myeloid leukemia is a unique disease that requires a different approach

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Chronic myelogenous leukemia (CML) in children is relatively rare. Because of a lack of robust clinical study evidence, management of CML in children is not standardized and often follows guidelines developed for adults. Children and young adults tend to have a more aggressive clinical presentation than older adults, and prognostic scores for adult CML do not apply to children. CML in children has been considered to have the same biology as in adults, but recent data indicate that some genetic differences exist in pediatric and adult CML. Because children with CML may receive tyrosine kinase inhibitor (TKI) therapy for many decades, and are exposed to TKIs during a period of active growth, morbidities in children with CML may be distinct from those in adults and require careful monitoring. Aggressive strategies, such as eradication of CML stem cells with limited duration and intensive regimens of chemotherapy and TKIs, may be more advantageous in children as a way to avoid lifelong exposure to TKIs and their associated adverse effects. Blood and marrow transplantation in pediatric CML is currently indicated only for recurrent progressive disease, and the acute and long-term toxicities of this option should be carefully evaluated against the complications associated with lifelong use of TKIs. (*Blood*. 2016; 127(4):392-399)

Introduction

The median age at diagnosis of chronic myelogenous leukemia (CML) is 60 to 65 years in Western registries,[1] and CML is rare among children and adolescents. CML constitutes 2% of all leukemias in children younger than 15 years and 9% of all leukemias in adolescents between 15 and 19 years, with an annual incidence of 1 and 2.2 cases per million in these 2 age groups, respectively.[2] Because of the low incidence of CML and a lack of robust clinical trial data in children and adolescents, practice standards for the management of pediatric CML are not as established as for adult patients.[3]

After the introduction of the tyrosine kinase inhibitor (TKI) imatinib approximately 15 years ago,[4] the treatment paradigm for CML changed considerably. The second-generation TKIs[5,6] dasatinib and nilotinib produce more rapid and deeper molecular responses compared with imatinib in adults. These second-generation TKIs are now included as first-line treatments for chronic phase CML (CML-CP) in the most recent adult CML guidelines from European Leukemia Net (ELN)[7] and the National Comprehensive Cancer Network (NCCN).[8] Continuing TKI treatment indefinitely has become a standard practice for adult patients with CML-CP, and the feasibility of discontinuing TKI in patients who achieve complete molecular remission (CMR) is also being explored.[9] Indications for hematopoietic stem cell transplant (HSCT), the only established curative treatment of CML, are now very limited.

Many pediatric oncologists follow treatment guidelines that are designed for adult patients, despite the absence of data supporting the extrapolation of adult guidelines to children. In some countries, children with CML are treated by adult oncologists. Yet, there are clear differences between CML in children and adults in terms of disease presentation and progression, along with differences in the underlying CML biology and host factors, which should be considered when treating pediatric patients with CML.

Differences in adult and pediatric CML may be related to host factors and CML leukemia cell biology

A number of studies have reported clinical findings in children[3,10,11] and young adults[12] with CML that suggest either a different leukemia cell or host biology compared with CML in adults.[13] Although it might be reasonable to assume that CML in an 8-month-old,[11] which may also involve congenital factors, will have a different biology from CML in a 70-year-old, there is little data to support this, and the biology of CML in children has been assumed to be identical to that in adults. It is clear that there are also host differences in adult patients compared with young, rapidly developing pediatric and adolescent patients that may affect CML development, response to treatment, and adverse effects of treatment.

CML biology is different in pediatric and adult disease

Both pediatric and adult patients with CML have the fusion gene *BCR-ABL1*, with breakpoints occurring in the same major breakpoint cluster regions (M-BCR) in the *BCR* gene on chromosome 22 and

Submitted June 5, 2015; accepted October 23, 2015. Prepublished online as *Blood* First Edition paper, October 28, 2015; DOI 10.1182/blood-2015-06-648667.

dispersed over a wide intronic distance (covering >200 kb) in the *ABL1* gene.[14] Krumbholz et al have shown that breakpoint distribution in BCR is different in pediatric CML compared with adult CML.[15] Given the different incidences of CML in children and adolescents vs adult patients, it is possible that distinct mechanisms account for initiation of chromosomal translocation in each cohort. On the genomic level, children with CML-CP exhibit a different breakpoint distribution pattern in the *BCR* gene and a higher proportion of breakpoints within *Alu* repeat regions compared with adults with CML-CP. DNA fusion sites within the *BCR* major breakpoint cluster region are significantly enriched in the centromere in adult CML, whereas pediatric CML exhibits a second cluster in the telomeres, largely overlapping with an extended *Alu* repeat region.[15] The latter distribution is similar to the pattern observed in adult Philadelphia-positive acute lymphoblastic leukemia (Ph^+ ALL) with M-BCR rearrangement.[16,17] These differences in the genomic landscape may contribute to the more aggressive clinical characteristics in pediatric CML compared with adult CML.

Within the M-BCR, the vast majority of CML patients exhibit transcript phenotypes with an e13a2 or an e14a2 junction (b2a2 and b3a2, respectively, in older nomenclature). Both RNA variants can occur either alone or simultaneously depending on alternative splicing of the e14a2 transcript, which is influenced by intronic and exonic DNA polymorphisms.[16-18] There are conflicting reports on the influence of these transcript phenotypes on hematologic findings at diagnosis. The majority of,[13] but not all,[12] studies in adults with CML showed that high platelet counts are observed more often in patients expressing the e14a2 transcript. Similar studies using small cohorts of pediatric patients with CML[19,20] found no clear patterns; however, transcript variants in pediatric patients were comparable with those in adults in a larger series that included 146 pediatric patients.[13]

The transcript phenotype also exerts an influence on the kinetics of treatment response to TKIs.[21] The clinical significance of transcript type on the rate of response to imatinib was evaluated in a large cohort of adult patients in CP, of whom 44%, 41%, and 14% exhibited e14a2, e13a2, and both transcripts, respectively. Hanfstein et al found a significant difference in median time to achieve a major molecular response (MMR) with imatinib in adult patients (n = 1105) with different transcripts. Patients who had the e13a2 transcript had significantly longer median time to MMR (18.4 months) compared with those with e14a2 (14.2 months).[22] Suttorp et al also found a faster response to imatinib in patients harboring the e14a2 transcript in a small cohort of children with CML.[23] Although the reason for these findings remains open to speculation (eg, higher immunogenicity of the additional 25 amino acid residues encoded by exon e14), further analysis of transcript types in children with CML is needed to validate these findings and evaluate the potential role in guiding management decisions.

Clinical presentation and disease progression are different in adult and pediatric CML

Children and adolescents, as well as young adults,[12] in CML-CP tend to have clinical presentations with more aggressive features,[12,24,25] although the impact on prognosis is debatable. The characteristics of pediatric CML have been reported in several studies, summarized in Table 1.[12,24-28] The proportion of pediatric patients diagnosed with advanced-stage disease (accelerated phase [AP] or blast phase [BP]) is higher than for adult patients.[3,10,11,29,30] Among children, the median size of the spleen is 8 cm below the costal margin (range, 0-25 cm).[11] This number is not very different from that of adults[31]; however, it is proportionally larger in children because the age-based normal size of the spleen in children is smaller than in adults. The median baseline white blood cell count in children with CML was approximately 250×10^9/L in an international registry of 200 children with CML (median age, 11.6 years [range, 8 months to 18 years]),[11] which is higher than the range of 80×10^9/L to 150×10^9/L in adults.[32] The disease maintains these aggressive clinical features after childhood, with young adults presenting with more aggressive disease compared with those diagnosed as older adults. The GIMEMA CML Working Party recently analyzed 2784 patients ≥18 years of age[25] and found that young adults (18-29 years) had splenomegaly and a larger spleen more often than did older adults.[25] In addition, young adults had lower complete cytogenetic response and MMR rates compared with older adults.[25] In a study by Millot et al, a higher proportion of children treated with imatinib failed to achieve BCR-ABL1 transcript levels ≤10% compared with adult patients.[27] It remains to be determined whether second-generation TKIs can achieve better response rates. Efficacy of nilotinib and dasatinib in children with newly diagnosed CML has been studied in phase 2 trials but the results have not been published (Table 2).[33-38]

Existing prognostic scores used in adults do not apply to children with CML

The Sokal, Hasford, and EUTOS scores are used to predict the outcomes of adult CML patients[32,39,40] and to guide treatment. The Sokal score[39] was established using cohorts treated with busulfan or hydroxyurea, whereas the Hasford score[32] was considered to be the best predictor of survival in patients on interferon α. More recently, the EUTOS score[40] was implemented as a simple calculation using just 2 parameters (spleen size and percentage of blood basophils) to categorize patients as low- or high-risk and predict progression-free survival based on the surrogate marker of early cytogenetic response to imatinib at 18 months. The Sokal and Hasford scores predict molecular response, risk of progression to AP or BP, and overall survival in adult patients treated with imatinib, and thus remain useful as prognostic markers in the TKI era.

NCCN guidelines (version 1.2015) recommend the use of dasatinib or nilotinib in intermediate- or high-risk patients based on the Sokal score or Hasford score.[8] Yet, the validity of these scores has not been formally evaluated in the pediatric population and their prognostic significance may not apply to these patients. The Sokal[39] and Hasford[32] scores were defined in cohorts that included small numbers of children and adolescents, and the EUTOS score[40] was derived using only data from adults (≥18 years). Using the Sokal score,[39] which is based on age, spleen size, platelet counts, and blast count, a 10-year-old with CML would have a lower risk than a 60-year-old patient with the same spleen size and blood cell counts. No data support this conclusion. The difference in spleen size by age in children should be taken into consideration when applying prognostic scores for CML. Suttorp et al attempted to validate the 3 scoring systems, as well as a modified "Sokal young score,"[41] in 90 children (median age, 11.6 years [range, 1-18) on imatinib.[26] There was high discordance among the 4 scoring methods, which validates the concerns raised about using these scores for risk assessment or to make treatment decisions for children with CML.

In adult patients, early molecular and cytogenetic response has been shown to correlate with long-term survival.[42] Millot et al evaluated the significance of early response in 40 children with newly diagnosed CML who were treated with imatinib,[27] and the result was comparable with that in adult patients.[42] Children with a BCR-ABL1/ABL

Table 1. Comparison of age-dependent differences in CML characteristics

			Organomegaly	Blood counts (median)				Transcript phenotype	Risk profiles			Outcomes	
Ref.	Cohort age (y)*	Patients (No.)	Median spleen size (cm BCM)	WBC (cells/μL)	Platelets (cells/μL)	Hgb (g/dL)	Blasts in PB (%)	b3a2† (%)	High-risk Sokal score (%)	High-risk EUTOS score (%)	CCA (%)	CML progression‡ (%)	Response to treatment at defined time point after start of TKI
26	1-18	72	6	217	405	10.0	1	n.r.	16	19	n.r.	n.a.	<10% at 3 mo: 64%§
27	0.8-16.7	25	5	252	n.r.	n.r.	n.r.	n.r.	52	n.r.	n.r.	0.0	<10% at 3 mo: 63%§
	1.9-17.3	15	13	378	n.r.	n.r.	n.r.	n.r.	80	n.r.	n.r.	13.3	>10% at 3 mo: 37%§
28	2.8-17.9	47	n.r.	171	577	9.9	n.r.	72	n.r.	n.r.	n.r.	3.0	CCyR at 12 mo: 96% MMR at 12 mo: 67%
12	16-29	120	5	144	430	11.1	2	52	26	18	6	8.7	>10% at 3 mo: 42%§
	30-44	383	3	106	369	11.8	1	61	24	16	4	7.3	>10% at 3 mo: 42%§
	45-59	495	1	74	364	12.6	1	58	22	11	5	5.3	>10% at 3 mo: 26%§
	>60	526	0	57	381	12.5	0	62	24	8	3	6.1	>10% at 3 mo: 25%§
24	15-28	61	39%‖	30.5	332	12.2	0	n.r.	3	8	5	n.r.	CCyR at 12 mo: 83% MMR at 18 mo: 65% CMR 23%¶
	30-85	407	23%‖	27.4	343	12.3	0	n.r,	8	n.r.	4	n.r.	CCyR at 12 mo: 88% MMR at 18 mo: 78% CMR 41%¶
25	18-30	329	4.5	62	370	11.8	1	54	20	18	4	14	CCyR at 60 mo: 80% MMR at 60 mo: 71%
	30-39	444	5.0	66	355	12.1	1	44	15	9	5	5	CCyR at 60 mo: 90% MMR at 60 mo: 86%
	40-49	613	3.0	54	380	12.0	1		21	9			
	50-59	693	2.0	57	350	12.2	1		25	10			
	60-69	473	1.8	54	333	12.3	1	47	28	6	3	5	CCyR at 60 mo: 90%
	>70	232	1.0	71	345	12.1	0.7		36	5			MMR at 60 mo: 88%

BCM, below costal margin; CCA, complex cytogenetic aberrations in addition to Philadelphia chromosome; CCyR, complete cytogenetic response (no Ph+ chromosome detectable); CML, chronic myelogenous leukemia; CMR, complete molecular response (no BCR-ABL1 transcript detectable by RT-PCR; for details on sensitivity of PCR see text of referred publication); EUTOS, European Treatment and Outcome Study; Hgb, hemoglobin; MMR, major molecular response (transcript ratio BCR-ABL1/ABL1 < 0.1%); PB, peripheral blood; n.a., not applicable because of short follow-up; n.r., not reported; TKI, tyrosine kinase inhibitor; WBC, white blood cells.

*Only trials reporting on cohorts of >30 patients and adult trials with data presented by age cohorts are included in the table.

†The percentage of patients showing both transcripts (b3a2 and b2a2) was added to the cohort expressing only transcript b3a2.

‡Length of follow-up time differs among the trials, thus age-dependent comparisons can only be made for subcohorts within a given trial.

§Percentage of the cohort achieving a transcript ratio higher or lower (as indicated) than 10% BCR-ABL1/ABL1 at month 3.

‖Proportion of patients with enlarged spleen of any measured size.

¶Includes patients who were treated with second-generation TKIs.

Table 2. Studies of TKI therapy for pediatric CML

TKI	Sponsor and collaborator	Phase	Year published	Author and references
Imatinib	COG	1	2004	Champagne[33]
Imatinib	COG	2	2012	Champagne[34]
Imatinib	French	4	2011	Millot[35]
Dasatinib	COG	1	2011	Aplenc[36]
Dasatinib	BMS/ITCC	1	2013	Zwaan[37]
Dasatinib	BMS	2	Unpublished	www.clinicaltrials.gov (#NCT00777036)[38]
Nilotinib	Novartis	1	Unpublished	www.clinicaltrials.gov (#NCT01077544)
Nilotinib	Novartis/COG/ITCC	2	Unpublished	www.clinicaltrials.gov (#NCT01844765)

BMS, Bristol-Myers Squibb; CML, chronic myelogenous leukemia; COG, Children's Oncology Group; ITCC, Innovative Therapies for Children with Cancer Consortium.

ratio ≤10% after 3 months of imatinib had higher rates of complete cytogenetic response and MMR at 12 months than did patients with a BCR-ABL1/ABL ratio >10%. This finding needs to be confirmed in a larger cohort of pediatric patients, but the early response could identify a subset of patients who require alternative treatment strategies.[27]

Host factors may underlie the different TKI adverse effects seen in children with CML

Imatinib is known to have several off-target effects[43] and has been shown to dysregulate bone remodeling and change bone mineral density in adult patients.[43,44] Children have immature skeletons and longer life expectancies than adult patients, and the current standard practice of continuing TKI indefinitely can lead to significant long-term morbidities in growing children, as has been shown in juvenile animal models.[45,46] In children, various groups have reported substantial growth abnormalities associated with imatinib in children with CML.[47-55] There is less experience with second- and third-generation TKIs in children, but dasatinib also seems to have a similar effect on growth.[48] It appears that prepubertal children are affected more significantly,[29] and though they may experience "catch-up" growth in puberty, their final height is lower than the predicted midparental height.[47] Some reports suggest that the growth hormone/IGF-1 axis is affected by TKIs,[45,48,56,57] and cotreatment with growth hormone or recombinant IGF-1 may improve the final adult height in children receiving TKIs; however, no study has demonstrated the safety or efficacy of this strategy.

TKIs may also have adverse effects on pregnancy outcomes because of the teratogenic potential of the drug.[58] Although the data are sparse,[8] it is generally recommended that female patients of childbearing age avoid pregnancy while taking a TKI and that TKI treatment should be withheld during pregnancy if the patient is in deep molecular remission.[58-61] It is strongly recommended that teenage girls with CML be counseled early about reproductive considerations to increase their adherence to long-term treatment.

Perhaps a more important question for children and adolescents with CML is whether TKI treatment has a long-term effect on future fertility. There is very little evidence on the effect of early TKI exposure on later fertility in humans, and the results of animal studies vary.[57,60,62,63] Nevertheless, a few case reports describe a decrease in markers of fertility in a teenage male[64] and a young adult female[65] who received imatinib. Studies with long-term follow-up in children treated with TKIs are needed.

Other morbidities observed in adults, such as thyroid dysfunction[66] and cardiovascular toxicity,[67-69] have not been reported in children to date; however, because children with CML may receive TKI therapy for much longer periods of time than adults, they may also develop unanticipated comorbidities, and careful follow-up is imperative. Although it will be important to gather more data in prospective studies, we recommend that pediatric patients who are treated with TKIs off protocol are at least monitored for height, weight, and Tanner stage on every visit, in addition to periodic bone age and dual-energy x-ray absorptiometry scans, and that an endocrinology consultation is pursued if there are abnormal patterns (Table 3).[3]

TKIs appear to cause immune dysfunction to some degree,[70] which interferes with routine immunizations in children. Live vaccines are not recommended.[3] It is safe to give inactivated vaccines, although humoral responses may be impaired, as in any immunocompromised patient.

Pediatric CML may require a different approach to TKI treatment

The goals of CML therapy are the same for adults and children: disease remission, reduced risk of progression, and survival.[71] However, the treatment of CML in children must take into account the added challenge of achieving these goals while minimizing toxicities for 6 or 7 decades. Although cure is the ideal goal for all patients regardless of age, for older adults, it may be sufficient to approach CML as a chronic disease, with the goal of maintaining patients in CML-CP for a few decades with TKIs. In the GIMEMA study,[25] the percentage of young adults who were treated with TKI and had cumulative probability of progression to AP and BP at 8 years was 16% (95% confidence interval [CI], 8-31), which was higher than in adults (5%; 95% CI, 3-8) or elderly (7%; 95% CI, 4-11). Children have a much longer life expectancy and thus potentially longer exposure to TKI therapy, yet there are no data on the long-term efficacy of TKI therapy beyond 15 years. Furthermore, as discussed before, prolonged treatment with TKIs has potentially major long-term effects and different effects in the still-growing child compared with the adult. These adverse effects can be cumulatively higher in the pediatric CML population with lifetime exposure to TKIs. Further complicating the issue are reports from pediatric oncologists who observe poor adherence more frequently in adolescents compared with older adults or younger children,[72,73] making extended use of TKIs a less viable option in these patients. When selecting a TKI, it is important to consider adherence. Twice-daily dosing of nilotinib may be more challenging for pediatric patients than once-daily dosing of imatinib or dasatinib. Formulations of TKI with

Table 3. Recommendations for monitoring and supportive care in children with CML receiving TKI therapy

- Accurate measurement of height and weight at each visit and close monitoring of growth velocity. Consider bone scan and DEXA scan and refer to endocrinology if there is evidence of an abnormal growth pattern.
- Tanner staging at each visit. Consider checking gonadotropins and sex steroids and refer to endocrinology if there is evidence of a pubertal delay.
- Thyroid function (TSH, free T4) 4 to 6 weeks after start of TKI and annually thereafter.
- Counseling on reproductive considerations for young women of childbearing age.
- Annual echocardiogram and electrocardiogram.
- Live vaccines are not recommended. Inactivated vaccines may be given safely, but their efficacy has not been proven.

DEXA, dual-energy x-ray absorptiometry; T4, thyroxine; TSH, thyroid-stimulating hormone.

Table 4. Results of HSCT in children (≤18 y of age) with CML in first chronic phase

Author	Year	Patients (No.)	Disease phase at HSCT	Donor source	Overall survival	Notes
Cwynarski[93]	2003	314	CP1, n = 253 Other, n = 61	MSD VUD	75% (CP1, MSD, n = 156) 65% (CP1, VUD, n = 97)	EBMT registry data
Suttorp[91]	2009	176	CP1, n = 158 Other, n = 18	MRD MUD	At 5 y: 87 ± 11% (MSD, n = 41) 52 ± 9% (MUD, n = 71) 45 ± 16% (MMD, n = 55)	
Muramatsu[94]	2010	125	CP1, n = 88 Other, n = 37	Unrelated	59.3% at 5 y	
Chaudhury[88]	2014	177	CP1 and hematologic remission		71% (95% CI, 65-77) at 5 y	CIBMTR data

Only studies with >100 cases are listed.

CI, confidence interval; CIBMTR, Center for International Blood and Marrow Transplant Research; CP1, first chronic phase; EBMT, European Group for Blood and Marrow Transplantation; HSCT, hematopoietic stem cell therapy; MMD, mismatched donor; MRD, matched-related donor; MSD, matched-sibling donor; MUD, matched-unrelated donor; VUD, volunteer-unrelated donor.

better palatability may also improve adherence among pediatric patients and should be developed. Other methods to improve adherence, such as direct supervision or various reminder systems,[74] may be needed in patients with suboptimal responses to TKIs. Another factor that needs to be considered is the cumulative cost of TKI therapy in children who may need decades of treatment, although this may become less of an issue in the near future with the introduction of generic products.[75]

Taking into account all of these issues, it is clear that an important goal of pediatric CML management should be the avoidance of lifelong treatment with TKIs. One potential solution is to stop TKIs after a certain period of deep molecular remission.[9,76-78] Use of this approach in children and adolescents with CML is supported by the results of the prospective Stop Imatinib (STIM) study in adults (≥18 years of age), which evaluated the feasibility of discontinuing imatinib in patients who maintained a CMR for at least 2 years on imatinib.[9] Sixty-nine of 100 patients enrolled had at least 12 months of follow-up (median, 24 months [range, 13-30]) and 42 of 69 patients (61%) experienced relapse. The probability of remaining in CMR at 12 months for these 69 patients was 41% (95% CI, 29-52). All patients who had a molecular relapse responded to reintroduction of imatinib. Despite these results, there is limited information on the longer-term (>5 years) outcomes of CML patients in CMR after cessation of TKI.[9,77] Intermittent TKI dosing[79] may be a potential approach to reducing long-term morbidity in pediatric CML while sustaining molecular remission.[46,54] More studies are needed to evaluate this approach.

Unfortunately, stopping TKI treatment in the subset of patients who are in molecular remission does not address the issue that the majority of children would probably need to remain on TKIs.[9] TKIs do not target the leukemic stem cells that may play a significant role in TKI resistance.[80-83] Because of the factors outlined here, there is a compelling argument for conducting trials in children and adolescents to study combinations of TKIs with other agents such as JAK2 inhibitors[83,84] and interferon-α[85,86] that do affect leukemic stem cells. With the goal of avoiding lifelong TKI treatment, strategies that permanently eliminate the CML clone—for example, using limited duration, more intensive chemotherapy in combination with TKIs, similar to approaches used in recent trials of Ph^+ ALL[87]—may be intriguing options for treatment of pediatric CML.

BMT for CML-CP may have a bigger role in children than in adults with CML

Until the availability of TKIs, blood and marrow transplantation (BMT) was once the optimal curative choice for children and adolescents with CML.[88] With its more aggressive clinical features and evidence of biological and host differences, pediatric CML cannot be easily categorized using adult criteria or treated using adult guidelines. As the only established therapeutic approach that can achieve a lifelong remission in CML, allogeneic BMT may allow pediatric CML patients to avoid lifelong TKI therapy. Until treatment approaches with TKIs, potentially in combination with other agents, can be optimized to achieve durable remission, BMT will continue to be considered the only curative option.

The risks vs benefits of BMT in children with CML can be viewed as similar to those for some nonmalignant diseases, such as sickle cell anemia or thalassemia, where the morbidity and mortality of long-term therapies to control the disease are weighed against the potentially more toxic, but curative modality of allogeneic BMT. Children with thalassemia are maintained on transfusion therapy and chelation therapy and can live for decades with low levels of toxicity and morbidity; however, cumulative side effects result in a shortened life span. Similarly, the risks of TKI, although low, include rare, serious, and life-threatening complications such as pancreatitis and pulmonary arterial hypertension. Surveys of patients with sickle cell disease give some insight into patient perceptions of the risks vs benefits of a higher risk curative therapy such as BMT weighed against maintenance with lower-toxicity but noncurative therapies such as TKIs: 72% of patients surveyed were willing to accept a ≥5% mortality risk and 57% were willing to accept a ≥10% risk of graft-versus-host disease (GVHD) to undergo curative HSCT.[89] With its long history, the complications of allogeneic BMT in younger patients have been well established and include acute and chronic GVHD, infertility, pulmonary fibrosis, endocrine failure, growth and development issues, and metabolic syndrome. Although it may be preferable to wait until patients reach the age of legal majority, transplant-related mortality (TRM) increases as early as 16 years of age[90] for umbilical cord blood donor BMT, which shrinks the window for decision-making.

The current outcomes of BMT for CML-CP in adults and children has been reported to be as high as 90% in a few studies,[91,92] whereas other studies showed lower numbers (Table 4).[88,91,93,94] Late outcomes of BMT (>2 years) for CML have been evaluated in the Bone Marrow Transplant Survivor study,[95] although only 5% of the patients were <21 years of age. In that study, overall health was excellent, very good, or good in 78% of patients. The major factors associated with long-term complications were chronic GVHD and, to a lesser extent, use of an unrelated donor.[95]

Since the advent of the TKIs, however, the application of allogeneic BMT in pediatric and adolescent patients has decreased dramatically because of a decrease in early complications associated with TKIs compared with BMT. Yet the complications of allogeneic BMT have also decreased since 2000, with better management of sinusoidal obstruction

syndrome, infections, and GVHD.[96] Nevertheless, patients who undergo BMT have a distinct risk of mortality associated with the procedure. The 1-year TRM for higher-risk acute leukemia in CR is 10% and the TRM rate in the CML IV study[92] was 7% (4/56) for allogeneic BMT in CR1. It should be pointed out that the median age for BMT patients in the CML IV study was 37 years and thus does not accurately represent the pediatric cohort. A recent paper on outcomes in a small group of pediatric patients with CML undergoing HSCT[28] reported a TRM of 0% after a median follow-up of 52 months. Moreover, the US Patient Survival Report from the Health Resources and Services Administration (HRSA) (http://bloodcell.transplant.hrsa.gov/research/transplant_data/us_tx_data/survival_data/survival.aspx) also reported a 100-day TRM of 0% for related donor BMT and 5% for unrelated donor BMT in patients with CML CR1 and <21 years of age. An increased use of reduced-intensity allogeneic BMT has resulted in a decrease in transplant-related mortality, although the risk of GVHD may be higher.[97] The use of alemtuzumab, antithymocyte globulin, and post-transplantation cyclophosphamide has also resulted in a significant decrease in both acute and chronic GVHD.[98-102]

With the current focus on the short-term responses to TKI and its few associated toxicities, there is no consensus on the role for allogeneic BMT, including human leukocyte antigen–identical sibling donor transplants, for CML-CP responsive to TKI therapy. Compliance and cost can limit access to TKI therapy, but donor availability for BMT is also an issue.

The field is ready to consider the possibility of long-term curative outcomes in pediatric CML, and accumulating evidence of the unique biology of the pediatric CML stem cell and host demand a re-evaluation of the role of single TKI as the optimal therapy and the possible role of BMT. The recent development of reduced-toxicity BMT, particularly human leukocyte antigen–identical sibling BMT, with its superior survival outcomes, may play a bigger role in the treatment of children with CML in the future. Unfortunately, there are no good prognostic criteria to identify pediatric CML-CP patients who have an expected event-free survival rate of <80% despite prolonged TKI treatment and who may benefit from BMT. For now, the only indications for allogeneic BMT in children and adolescents are for those who have failed TKI therapy, have experienced progression of CML while on a TKI, or have CML-BP. Better prognostic criteria for evaluating long-term survival and complications of CML-CP treated with TKI, as well as studies evaluating reduced-toxicity BMT for pediatric CML-CP, are needed.

Summary

CML in children has more aggressive clinical features, and recent work has begun to reveal differences in CML biology in adults and children that may account for the clinical differences in CML presentation, progression, and response to treatment. Clinicians need to be aware of the host factors in children that lead to different morbidities associated with TKI treatment. The prospect of decades-long TKI treatment raises the question of whether children in the first CML-CP should be offered BMT, but this should await further investigation. Clinical trials to test the feasibility of intermittent TKI therapy or stopping TKI treatment and to test new agents that target CML stem cells should be preferentially considered in children. International collaborative efforts and funding to conduct larger studies and construct a shared clinical database for pediatric CML are urgently needed to address unanswered questions and issues.

Acknowledgments

The authors thank Stacey Tobin for assistance in language editing and William J. Muller for valuable discussions regarding vaccination recommendations in immune compromised patients.

Authorship

Contribution: All authors wrote and edited the manuscript.

Conflict-of-interest disclosure: N.H. has served as an advisor for Pfizer and as a consultant for Sanofi. F.M. has served as an advisor for Pfizer and has been a speaker for ARIAD and Novartis. M.S. has received research funding from Novartis and Bristol-Myers Squibb and has provided expert testimony for Pfizer. The remaining authors declare no competing financial interests.

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