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Practice Patterns of Physician Treatment for Pediatric Chronic Myelogenous Leukemia

Jeffrey R. Andolina[1,*], Michael J. Burke[2], Nobuko Hijiya[3], Sonali Chaudhury[3], Kirk R. Schultz[4], Michael E. Roth[5]

[1] *Department of Pediatrics, Golisano Children's Hospital, University of Rochester Medical Center, Rochester, New York*
[2] *Department of Pediatrics, Children's Hospital of Wisconsin, Milwaukee, Wisconsin*
[3] *Division of Hematology/Oncology/Stem Cell Transplant, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, Illinois*
[4] *Department of Pediatrics, British Columbia Children's Hospital, British Columbia, Canada*
[5] *Department of Pediatrics, University of Texas M.D. Anderson Cancer Center, Houston, Texas*

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Chronic myelogenous leukemia (CML) is a rare disease in children for which pediatric evidence-based guidelines are lacking. We designed an anonymous survey for practicing pediatric oncologists and bone marrow transplantation (BMT) physicians to assess their willingness to recommend BMT for a patient with CML based on various clinical scenarios. A total of 274 physicians responded to the survey (13.4% response rate). Nearly all pediatric oncologists and BMT physicians recommended against BMT at time of diagnosis of CML in the chronic phase, with only 8.0% and 1.9% recommending BMT if a matched sibling donor (MSD) and a matched unrelated donor (MUD), respectively, was available. Similarly, after a first poor response to tyrosine kinase inhibitor (TKI) therapy or hematologic relapse, physicians continued to recommend against BMT (39.5% and 23.3% recommended BMT in patients with a matched sibling donor and matched unrelated donor, respectively). However, 81.7% and 69.8% of respondents would recommend BMT after 2 hematologic relapses on TKI therapy, if an MSD and an MUD, respectively, were available. In addition, there was great interest in developing a clinical trial evaluating the safety and efficacy of stopping TKIs in children with CML who achieve and maintain a deep molecular response, with 86.7% of respondents stating they would offer such a trial to their pediatric patients. This survey highlights the need for evidence-based, pediatric-specific guidelines for the management of children and adolescents with CML.

INTRODUCTION

Pediatric chronic myelogenous leukemia (CML) is rare, with an incidence of only 1 in 1 million, representing approximately 3% of pediatric leukemias [1]. The introduction and Food and Drug Administration approval of tyrosine kinase inhibitors (TKIs), first in 2001 for adults and then in 2006 for children, with imatinib (Gleevec), has resulted in their widespread use in children and adults with CML. TKI therapy, including first-generation imatinib and second-generation dasatinib and nilotinib, has been extremely effective in adult patients with chronic phase (CP) CML, with >95% long-term survival reported [2-4]. The life expectancy of newly diagnosed adults with CP CML now approaches that of the general population [5]. Although the data in children with CML receiving TKI therapy are limited, outstanding treatment responses and survival outcomes have been reported [6]. Nonetheless, , many concerns remain surrounding lifelong TKI administration and the associated toxicities in children, including growth retardation and possible cardiac toxicity [7,8].

Bone marrow transplantation (BMT) remains a curative therapy for CML for consideration in children. However, this cure comes at a cost, with both upfront and long-term morbidity and mortality. Data in the pre-TKI era show overall survival rates of 66% to 87% with matched sibling donor (MSD) BMT and 45% to 65% with matched unrelated donor (MUD) BMT [9-12]. In addition, chronic graft-versus-host-disease (GVHD) and transplantation-related late effects continue to affect up to one-half of survivors [13,14]. Data on BMT for CML are much more limited in the current TKI era. Chaudhury et al [15] retrospectively reviewed patients who underwent BMT between 2001 and 2010 and reported an overall survival of 75% and an event-free survival of 59% [15]. In addition, there were no survival differences in patients receiving pretransplantation TKI therapy [15].

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* Correspondence and reprint requests: Jeffrey R. Andolina, MD, 601 Elmwood Avenue, Box 777, Rochester, NY 14642.
E-mail address: Jeffrey_andolina@urmc.rochester.edu (J.R. Andolina).

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Discontinuation of TKI therapy in adult patients with CP CML who have achieved and maintained a prolonged deep molecular response (≥4.5 log reduction in BCR-ABL1) for 2 or more years has proven feasible, with approximately 40% to 50% of patients able to remain in a molecular remission off of TKI therapy [16-18]. However, discontinuation of TKI therapy in children with CML has not yet been formally studied, with only limited cases reported in the literature, mainly in the setting of noncompliance [19,20].

Established CML response criteria are outlined in Table 1, and general adult CML treatment guidelines are summarized in Table 2. Little has been published regarding the current practice patterns of pediatric oncologists and/or BMT physicians in children and adolescents diagnosed with CML. Owing to the rarity of pediatric CML, little data are available to help guide decision making. Guidelines and expert recommendations do exist, however [21-25]. Therefore, we set out to formally assess how pediatric oncologists and BMT physicians would manage children and adolescents with CML, presenting a variety of clinical scenarios with varied patient responses to TKI therapy to evaluate the decision to recommend indefinite TKI therapy versus BMT.

Table 2
Adult CML Treatment Guidelines, Adapted from National Comprehensive Cancer Network and European Society for Medical Oncology Recommendations [34,35]

Summary recommendations: Adult CP CML
Initial treatment for adult CP CML includes imatinib, bosutinib, dasatinib, or nilotinib. Consider clinical trial if available.
—
If patient meets response milestones, continue current TKI and monitor for side effects.
If patient has suboptimal response or failure, evaluate patient compliance and drug interactions. Consider kinase domain mutation analysis.
If patient has suboptimal response or failure, switch to alternate TKI. Consider evaluation for allogeneic stem cell transplantation.
At the time of treatment failure, patient should have a bone marrow evaluation to assess CML disease status and to evaluate for clonal evolution or progression to accelerated phase or blast crisis.
Allogeneic transplantation may be considered for selected patients with treatment failure.
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Discontinuation of TKI therapy appears to be safe in selected adults with CML. Adult patients must meet strict criteria to be considered eligible for TKI discontinuation, including sustained MR4 (4-log reduction in *Bcr/Abl1* transcript) for ≥2 years. More frequent monitoring is recommended. Adult patients should be thoroughly consented if considering TKI discontinuation.

MATERIALS AND METHODS

Survey Tool and Study Population

Pediatric oncologists and pediatric BMT physicians currently practicing in the United States and Canada were sent an e-mail inviting them to participate in an anonymous online survey pertaining to the management of children diagnosed with CML. Potential participants' e-mail addresses were obtained via PubMed and Google Scholar searches, academic institution websites, and hospital websites. A total of 2,038 pediatric oncologists and BMT physicians were invited to participate in the survey. Pediatric oncologists were not prescreened to determine whether they cared for patients with CML.

The survey tool focused on provider practices in the management of pediatric patients with CML, with the goal of understanding provider views on the role of BMT for these patients. Participants were presented with a variety of clinical cases in which the response to TKI therapy differed and then asked about the likelihood of recommending BMT over continuing TKI-only therapy (Supplementary Table 1). For each clinical scenario, providers were asked about the likelihood of recommending BMT if the patient had an HLA-identical MSD or a 10/10 HLA-matched MUD.

The survey tool was created by pediatric oncologists and BMT specialists participating in the CML Working Group within the Children's Oncology Group's Myeloid Disease Committee. The survey was piloted by pediatric oncologists and BMT specialists for question content and readability.

Bivariate associations between patient responses to TKI therapy and presence of an MSD with provider preferences for recommendations regarding BMT were evaluated using the χ^2 test in each of the clinical scenarios presented. Associations between provider demographics and provider recommendations for BMT were also assessed. Statistical significance was determined and noted as follows: $^*P < .05$; $^{**}P < .01$.

RESULTS

Demographics

A total of 2038 pediatric oncologists and pediatric BMT specialists were invited to participate in the survey. Among these, 274 physicians participated in the survey, for an overall response rate of 13.4%. The primary area of interest was identified as leukemia by 39% of respondents and as BMT by 14% (Table 3). Provider years in practice and experience in treating children and adolescents with CML varied, with 62.6% of respondents reporting treating fewer than 6 patients with CML in their career.

Provider Recommendations for BMT Based on Response to TKI Therapy

Survey responders were asked how likely they would be to recommend BMT for a patient with CP CML if the patient had a 10/10 HLA MSD or a 10/10 HLA MUD in 4 different scenarios: (1) a patient with optimal response to initial TKI therapy; (2) a patient with poor response to initial TKI therapy; (3) a patient with complete molecular response to initial TKI therapy but relapse at 3 years after initial diagnosis; and (4) a patient meeting criteria for treatment failure during a second course of TKI therapy. Few respondents recommended BMT for a patient with optimal response to initial TKI therapy with an MSD (8.0%) or an MUD (1.9%) (Figure 1). More than a one-third of responders recommended BMT for a patient with an initial poor response to TKI therapy (40.2%) and for a patient who relapsed during initial TKI therapy (36.5%) if an MSD was available, whereas approximately one-quarter of responders recommended BMT for a patient with poor response (31.4%) or relapse during initial TKI therapy (23.3%) if an MUD was the

Table 1
Time Landmarks and Response Criteria to TKI [21,32,33]

Time, mo	Failure	Suboptimal Response	Warnings
Diagnosis	NA	NA	High risk; del(9q-); additional cytogenetic abnormalities in Ph^+ cells
3	No HR; stable disease or disease progression	Less than CHR	NA
6	Less than CHR; no cytogenetic response; Ph^+ >95%	Less than PCyR; Ph^+ >35%	NA
12	Less than PCyR; Ph^+ >35%	Less than CCyR	Less than MMR
18	Less than CCyR	Less than MMR	NA
Any time	Loss of CHR; loss of CCyR; mutation (eg, T315I)	Additional cytogenetic abnormalities in Ph^+ cells; loss of MMR; mutation	Any rise in transcript level; additional cytogenetic abnormalities in Ph^- cells

NA, not applicable ; Ph, Philadelphia chromosome; HR, hematologic response; CHR, complete hematologic response; PCyR, partial cytogenetic response; CCyR, complete cytogenetic response; MMR, major molecular response.

Table 3
Respondents' Demographic Data

Characteristic	%	Number
Primary area of interest		
Leukemia	39.3	94
BMT	13.8	33
Solid tumors	20.9	50
Hematology	10.0	24
Other	15.9	38
Practice type		
Academic	80.4	193
Nonacademic	19.6	47
Number of children with CML personally treated		
0	3.8	9
1-5	58.8	141
6-10	25.0	60
11-15	6.7	16
>15	5.8	14
Years in practice as attending physician		
<5	24.7	59
5-10	24.3	58
11-20	20.9	50
>20	30.1	72

best available donor. The vast majority of respondents (81.7%) recommended BMT for a patient who met the response criteria for treatment failure during a second course of TKI therapy if an MSD was available, compared with 69.8% if only an MUD was available. In each of the 4 scenarios, responders were significantly more likely to recommend BMT if the patient had an MSD compared with an MUD ($P < .05$). In addition, respondents were significantly more likely to recommend BMT for patients with poor response or relapse on a first course of TKI compared with patients with an optimal response ($P < .001$), irrespective of whether either an MSD or MUD was available. Similarly, participants were also significantly more likely to recommend BMT for patients with failure of a second course of TKI compared with either a poor response to or relapse after the first course of TKI ($P < .001$), irrespective of whether either an MSD or an MUD was available (Figure 1).

Association of Provider Demographic Factors with Recommendations for BMT

Associations among provider experience in caring for pediatric patients with CML, years in practice, and provider subspecialty (oncology versus BMT) were assessed for preferences in recommending BMT. A provider's experience in managing children and adolescents with CML was not significantly associated with recommendations for BMT except in the scenario where a patient has an available MSD and had relapsed on an initial course of TKI (Figure 2A and B). However, survey responders who had in practice as an attending physician for >10 years were more likely that those with <10 years of experience to recommend BMT for a patient with an MSD who had a poor response to initial TKI therapy (46.7% versus 31.6%; P = .02) or relapsed during initial TKI therapy (42.6% versus 28.2%; $P = .02$) (Figure 2C and D).

Given that leukemia specialists and BMT specialists are the health care providers most commonly involved in the decision making regarding offering BMT for patients with CML, we analyzed their management preferences separately. Less than one-third of leukemia specialists would recommend BMT to a patient with CP CML who received first-line TKI therapy, irrespective of whether an MSD was available and irrespective of the response to initial TKI (Figure 2E and F). BMT specialists were significantly more likely than leukemia specialists to recommend BMT in most of the case scenarios, including 40% to 50% of BMT physicians who would recommend BMT after a

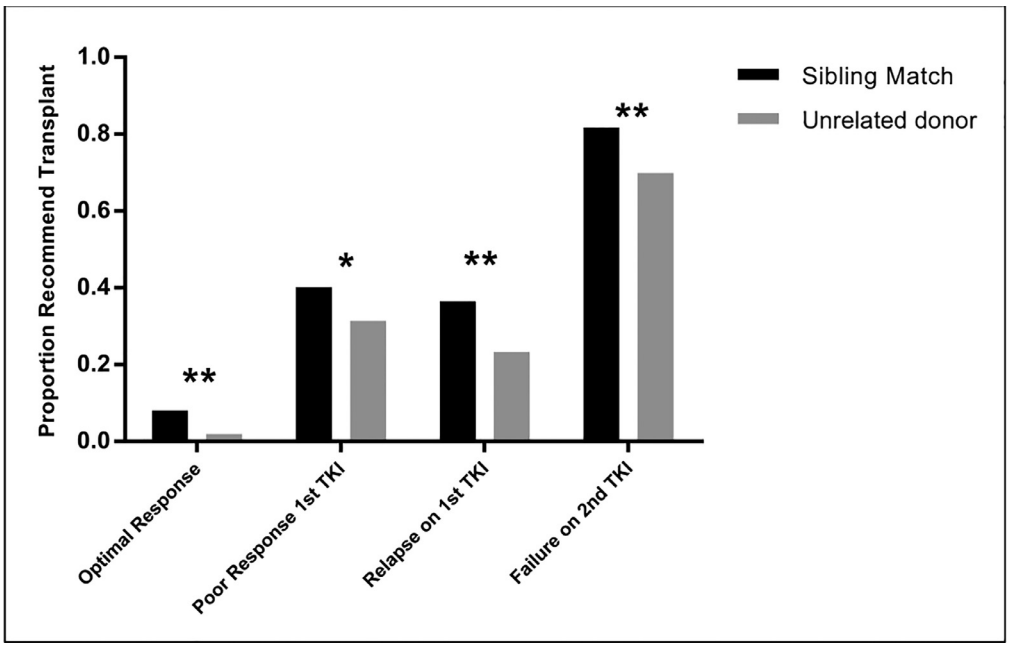

Figure 1. Provider recommendations for BMT based on response to TKI therapy. The proportion of respondents who would recommend BMT for 4 different TKI response scenarios is categorized by the availability of an MSD or an MUD. *$P < .05$; **$P < .01$.

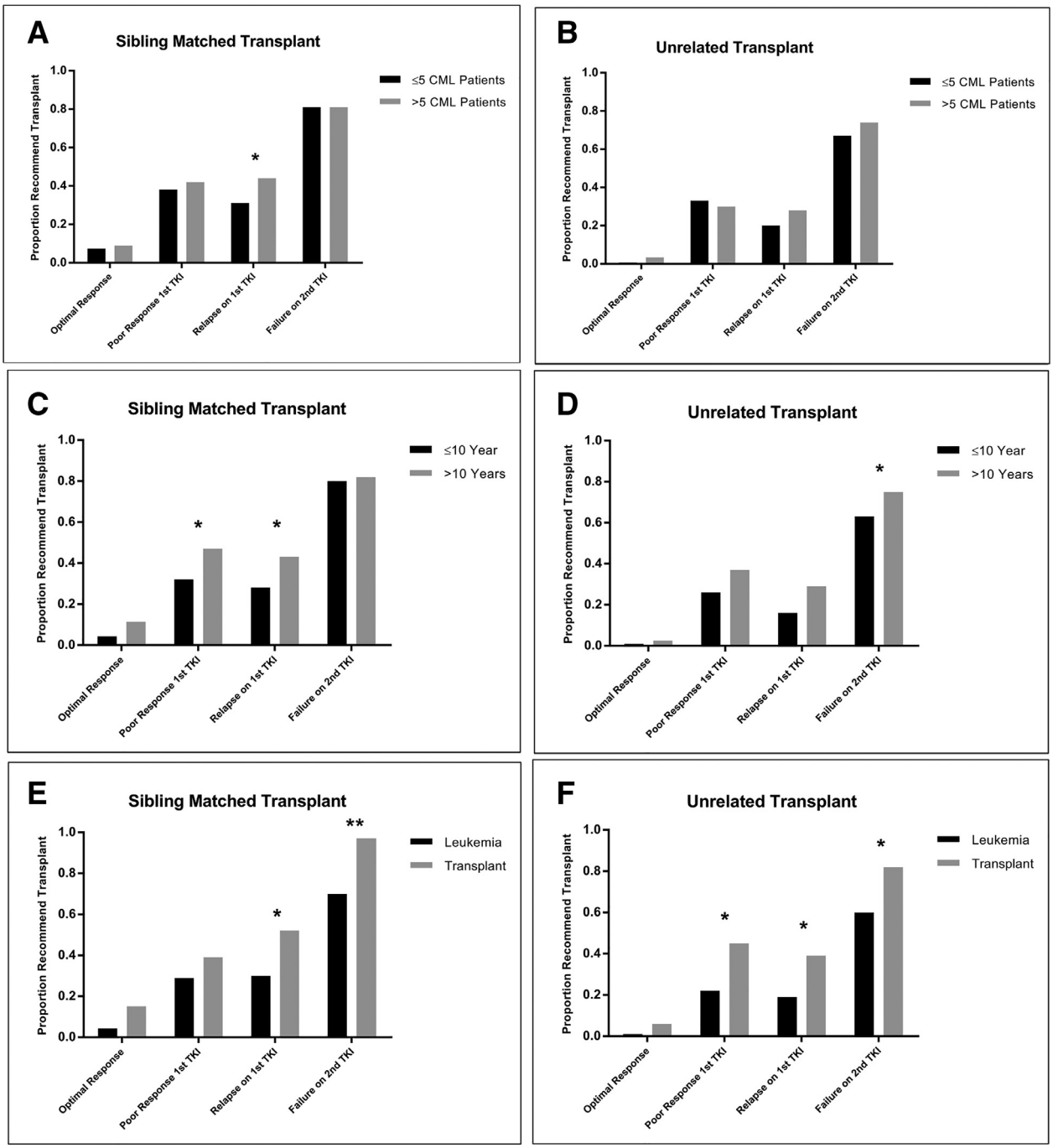

Figure 2. Associations of provider demographic factors with recommendations for BMT. The proportion of respondents who would recommend BMT for 4 different TKI response scenarios, categorized by the number of patients with CML treated (A and B), years in practice (C and D), and primary subspecialty, leukemia versus BMT (E and F). $^{*}P < .05$; $^{**}P < .01$.

suboptimal response or relapse during an initial TKI therapy (Figure 2E and F).

Provider Preferences for TKI Therapy and Interest in Stopping TKIs

Given the variety of TKIs currently available, survey responders were asked which TKI they would start in a patient with newly diagnosed CP CML. Two-thirds of the physicians (67.4%; 61.7% of leukemia specialists versus 69.7% of BMT specialists) responded they would start imatinib, and an additional 30.1% (34.0% of leukemia specialists versus 30.3% of BMT specialists) would start dasatinib (Figure 3). Preference regarding the selection of initial TKI was not associated with years in practice or total number of CML patients treated.

Several studies in adult patients with CP CML who have achieved and maintained optimal responses to TKI therapy (at least a 4- to 4.5-log reduction in BCR-ABL1 by quantitative RT-PCR) have demonstrated that TKI therapy can be safely stopped in a significant proportion of patients (~40%). Our survey assessed the responders' willingness to stop TKI therapy in a teenage patient who had maintained a molecular response with a 4.5-log reduction from diagnosis (MR4.5) for >2 years.

Thirty percent of responders (30.8%; 26.6% of leukemia specialists versus 41.2% of BMT specialists) reported they would consider stopping TKI in this scenario, even outside the context of a clinical trial, and one-half of responders (52.9%; 55.3% of leukemia specialists versus 32.4% of BMT specialists) reported that they would consider stopping TKI therapy only in the context of a clinical trial (Figure 4A). Participants were subsequently asked whether they would consider participating in a clinical trial to assess the feasibility of stopping TKI therapy in children and adolescents with CP CML who achieved a sustained MR4.5 for >2 years,. The vast majority of pediatric oncologists and BMT physicians (86.7%; 85.1% of leukemia specialists versus 84.8% of BMT specialists) responded that they would offer a TKI stopping study to their eligible patients (Figure 4B).

DISCUSSION

We surveyed a large group of pediatric oncologists and pediatric BMT physicians from pediatric centers across North America, receiving a cross-section of respondents who care for children with CML. The median respondent was from an academic center in the United States and had cared for relatively few children with CML. To our knowledge, this is the first large-scale formal assessment of CML management in children to determine the role of BMT in the TKI era. Several important themes emerge from our study results. First, the survey results strongly suggest that children with CP CML are managed primarily with indefinite TKI therapy. This is true regardless of the available BMT donor at diagnosis. In addition, after a poor response or relapse during TKI therapy, the majority of pediatric oncologists and BMT physicians would not recommend BMT, but instead would recommend switching to a second TKI. Thus, these results suggest that in these 2 clinical scenarios, children with CML are managed more in line with the adult practice of indefinite TKI therapy [26].

The survey responses that we collected in this report appear to reflect management recommendations that have changed over the past 10 years. Burke et al [27] performed a similar survey of pediatric oncologists and BMT physicians in 2009 surrounding the management of Philadelphia chromosome-positive leukemias (CML and acute lymphoblastic leukemia), receiving responses from 27 of the 32 experts solicited. They found that 63% of respondents recommended BMT with an MSD for patients with CP CML in first complete remission [27]. Our differing results likely reflect the growing comfort with prolonged TKI therapy in children with CML. Our survey results show that only after treatment failure of 2 separate courses of TKI would the majority of pediatric providers recommend BMT with the best available donor. Based on our results, it appears that most pediatric providers view BMT for pediatric CML as an option reserved only for patients with multiple relapses. Our survey findings are similar to more recent pediatric CML guidelines, which recommend BMT only after failure of first- and second-generation TKI [21,24]. Other current expert recommendations for pediatric CML do not provide clear criteria on when to proceed with BMT in patients receiving TKI therapy, with most recommending consideration of BMT in those with poor response or toxicity [22,23,25].

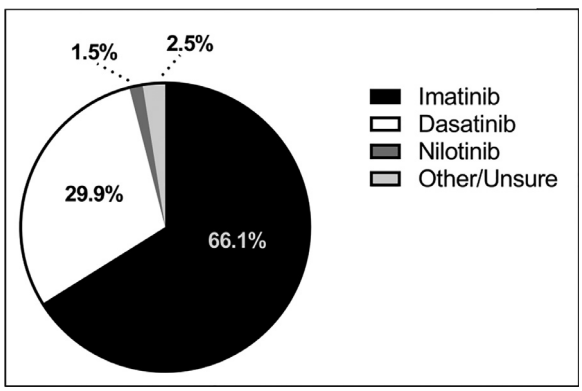

Figure 3. Initial TKI of choice for pediatric CP CML.

Our survey identified that physician demographics were associated with differential practice preferences. Transplantation physicians were more likely than their oncology counterparts to recommend BMT in all clinical scenarios. In addition, physicians in practice for >10 years were more likely than less experienced physicians to recommend BMT across all scenarios, which may reflect practicing during a period in which TKI therapy was not as prevalent as it is today.

The majority of survey responders (66.1%) recommended imatinib as the up-front TKI of choice, whereas a significant minority recommended starting with dasatinib. Both drugs have now received Food and Drug Administration approval for use in children, with the addition of dasatinib as of 2017. The initial TKI agent continues to be a subject of debate for pediatric CML providers. Data in adults with CP CML has shown more rapid responses, although no overall survival improvement, with second-generation TKIs such as dasatinib, and many adult CML experts now recommend starting with either a second-generation TKI or imatinib [26,28,29]. In our survey, 29.9% of pediatric oncologists recommended dasatinib at initial diagnosis for their pediatric and young adult patients. Pediatric data with dasatinib and nilotinib are limited; however, these TKIs appear to be safe and effective in children [30,31].

Finally, there appears to be significant interest in developing a pediatric TKI stopping clinical trial, with 86.7% of respondents reporting that they would offer such a study to their eligible patients. Discontinuation of TKI therapy in patients with CP CML who have achieved a complete molecular response has not been formally studied in children as it has been in adults with CML, although previous case series in children have shown that it may be feasible [19,20]. Further, almost one-third of physicians reported they would consider stopping TKI therapy in selected patients outside of a clinical trial. Given the potential long-term toxicities of TKIs, as well as the significant challenges surrounding adherence in adolescents and young adults with CML, evaluating the safety and feasibility of TKI discontinuation is of critical importance.

This study has several limitations. Survey participants were asked about their management of children and adolescents with CML in hypothetical case scenarios, and their responses might not be fully representative of their practices. Although the survey was designed to assess providers' recommendations for BMT, it did not explore the reasons behind these decisions. Thus, the extent to which providers were concerned about the toxicity of long-term TKI therapy, and how those concerns may have affected their management decisions, are unclear. Finally, although the overall survey response rate was <20%, it is important to note that the survey was sent to all pediatric hematology/oncology providers, and thus many providers likely elected to not participate in the survey because they do not care for patients with CML.

Our present results demonstrate the changing landscape of pediatric CP CML, for which indefinite TKI therapy is now the de facto treatment of choice for the vast majority of pediatric oncologists and BMT physicians. Only after multiple relapses would most pediatric physicians recommend a

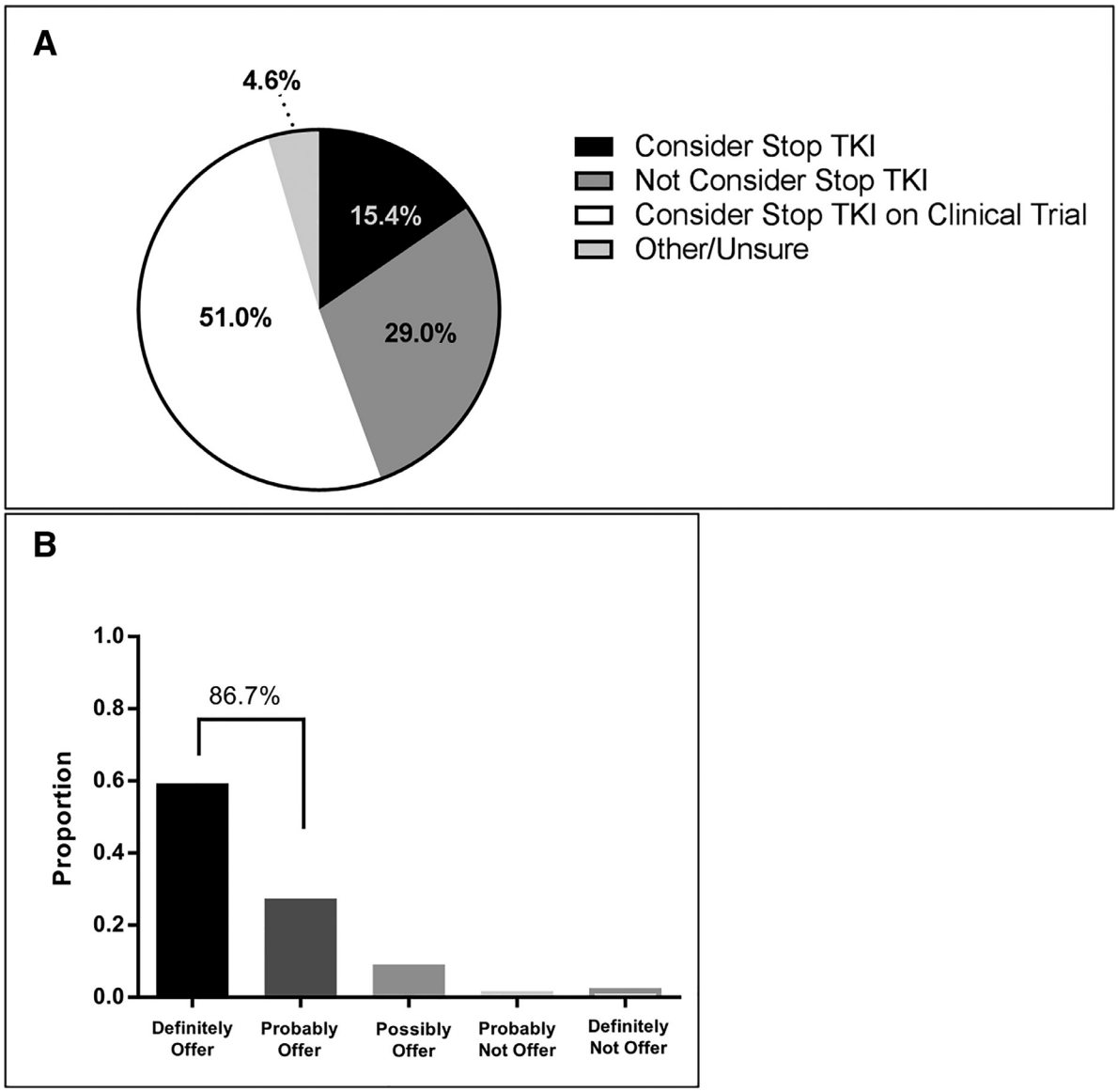

Figure 4. Providers' in stopping TKI therapy. (A) Providers' willingness to stop TKI in a teenage patient who had maintained an MR4.5 for >2 years. (B) Providers' willingness to enroll a patient on an open clinical trial assessing the feasibility of stopping TKI therapy in children and adolescents with CP CML who achieved a sustained MR4.5 for >2 years.

referral to BMT. In addition, our results highlight the need for pediatric-specific guidelines for CP CML from such entities as the National Comprehensive Cancer Network or European LeukemiaNet. Our hope is that evidence-based pediatric-specific expert recommendations and prospective multi-institutional trials may pave the way for improved outcomes in pediatric CML.

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SUPPLEMENTARY DATA

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