

Review

Update in Childhood Chronic Myeloid Leukemia

Fiorina Giona *  and Simona Bianchi

Department of Translational and Precision Medicine, Sapienza University of Rome, Via Benevento 6, 00161 Rome, Italy

* Correspondence: fiorina.giona@uniroma1.it

Abstract: Chronic myeloid leukemia (CML) in childhood represents only 3% of newly diagnosed pediatric leukemia. The diagnostic hallmark of CML is the Philadelphia (Ph) chromosome, which derives from the fusion of the *ABL1*-oncogene located on chromosome 9 to the breakpoint cluster region (*BCR*) gene on chromosome 22, resulting in a constitutively dysregulated *ABL1* tyrosine kinase, either as 210 kDa or 190 kDa. Depending on the localization of the breakpoint site within the major *BCR* region, the majority of CML patients exhibit transcripts with either the b3a2 or b2a2 junction, or both. Several questions are still open with regard to childhood CML, especially concerning the biologic and clinical features of the disease, and the treatment of choice for pediatric patients with CML. Moreover, over the last few years, several tyrosine kinase inhibitors (TKIs) have been available for children and adolescents with CML, and current clinical practice investigates what the effective and optimal doses of TKIs are in these two categories of patients. The use of TKIs in pediatric patients with CML has also opened up questions on the following items: (1) the long-term effects of these drugs on children; (2) the management of pediatric CML forms resistant or intolerant to TKIs; (3) the monitoring of disease outcomes during treatment; (4) and the right timing to discontinue therapy. Despite the efficacy of TKIs also in the pediatric population, the potential late adverse effects, and the drug resistance, leave open the possibility of allogeneic hematopoietic stem cell transplantation as a treatment option in pediatric CML. Published data and personal experiences regarding these issues will be analyzed and discussed.

Keywords: CML; children and adolescents; treatment approaches; TKI; HSCT

**Citation:** Giona, F.; Bianchi, S.Update in Childhood Chronic Myeloid Leukemia. *Hemato* **2022**, *3*, 718–730. <https://doi.org/10.3390/hemato3040048>

Academic Editors: Domenico Russo, Gianantonio Rosti, Francesco Onida and Jane Apperley

Received: 30 September 2022

Accepted: 27 October 2022

Published: 5 November 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Chronic myeloid leukemia (CML) is rare in children and adolescents, accounting for 2 and 9% of all leukemias in children less than 15 years of age and in adolescents between 15 and 19 years. The annual incidence increases with age: from 1 per million in children younger than 15 years to 2.5 per million in adolescents [1]. CML is even rarer in infants [2]. Because of the rarity of CML in children, data on clinical and biological features are scarce before the era of TK inhibitors (TKIs). The advent of imatinib and second-generation TKIs (2GTKI) increased the interest in the biological and clinical knowledge of this disease even in children with CML and has dramatically changed the management and prognosis in this category of patients. Three TKIs, imatinib (IM), dasatinib (DASA), and nilotinib (NILO), are currently available for the treatment of children with CML. Most studies on the efficacy [3–6] and long-term side effects [7–11] focus on IM, as it was the first TKI approved for pediatric use, nearly two decades ago. There are no data that suggest superiority in terms of efficacy of one TKI over another. A small amount of data is available on the long-term side effects of DASA and NILO [12,13]. Many questions are still open regarding childhood CML, so in this review, we will try to answer the main biological, clinical, and therapeutic issues.

2. Are the Biologic and Clinical Features of CML the Same in Adults and Children?

Several studies have reported that children and adolescents tend to have a more aggressive clinical presentation than adults [14–17] probably due to either a different leukemia cell or host biology [2]. Nevertheless, children with CML share the same genetic features as adults: the balanced translocation t(9;22)(q34;q11), which leads to the fusion of the *ABL1*-oncogene located on chromosome 9 to the same breakpoint cluster regions in the *BCR* gene (M-BCR) on chromosome 22, resulting in a constitutively dysregulated *ABL1* tyrosine kinase, with either 210 kDa or 190 kDa. However, the breakpoint distribution in the *BCR* gene region has been reported to be different in childhood CML compared with adult CML [14]. The distribution pattern detected in children is similar to that observed in adult Philadelphia-positive acute lymphoblastic leukemia (Ph1 ALL) with M-BCR rearrangement [15,18–20]. Similarly to adults, almost all of the children and adolescents with CML exhibit e13a2 (b2a2) or/and e14a2 (b3a2) junctions.

Using a targeted deep next-generation sequencing (NGS), additional mutations to the *BCRABL1* fusion gene were identified in CML adults [21]. Recently, a higher incidence of mutated cancer driver genes has been found in CML children compared with CML adults [22]. Moreover, differentially expressed genes and pathways unique to pediatric CML were also reported [23]. These differences in the genomic landscape could contribute to the more aggressive clinical presentation in pediatric CML.

Several studies have demonstrated that the multistep leukemogenetic process, which requires many years to be completed, is necessary to induce a CML-CP [24]. However, reports of infant CML suggest that transformation events may occur over a short period of time in this category of patients, leading to a disease development similar to that observed in adult CML [2]. As in adults, three phases, chronic (CP), accelerated (AP), and blastic (BC), can be recognized in children and adolescents at diagnosis or during treatment. Most of the pediatric CML patients have a diagnosis in CP; however, the proportion of those diagnosed with an advanced phase is higher than in adults. A recent study from the “International Registry of Chronic Myeloid Leukemia in Children and Adolescents” reported 7.5% patients with de novo advanced phase out of 479 patients diagnosed with CML at age <18 years [25].

Concerning the clinical presentation, children with CML-CP tend to present a higher white blood cell count than adults, frequently combined with thrombocytosis (60%) and splenomegaly (70%). A study on a large pediatric series documented that in children, as in adults, specific *BCR/ABL1* transcript types are associated with distinct hematological alterations, such as a high platelet count with the e14a2 transcript [26]. In addition, an Italian cooperative study showed that a predominance of the e14a2 transcript type is associated with a platelet count significantly higher in girls than in boys [5]. A minority of children and adolescents can present symptoms of hyperviscosity, especially ocular symptoms and priapism [27,28].

3. Can the Prognostic Scores Used in Adults with CML Be Applied to Children?

The validity of the Sokal, Hasford, and EUTOS scores [28–31], which are used to predict the outcomes of CML adults and guide treatment, have not been formally evaluated in the pediatric population. Age, one of the prognostic factors taken into account in the Sokal score, and the spleen size are the limiting factors in applying these scores in this category of patients. Indeed, the difference in the spleen size by age in children has to be considered when applying prognostic scores for CML. One pediatric group attempted to retrospectively validate the three scoring systems, as well as a modified “Sokal young score”, in 90 patients younger than 18 years treated with imatinib. The high discordance found among these scoring methods supports the concerns about using them in the management of children with CML [32].

More recently, in the adult population, the EUTOS Long-Term Survival (ELTS) score was validated as a better predictive method of outcome than the previous scores [32–34]. The ELTS score was tested on 350 CP-CML children and adolescents treated with IM and

registered in the “International Registry of Chronic Myeloid Leukemia in Children and Adolescents”. Even in this retrospective study, the ELTS score was able to predict the outcome in children and adolescents with CP-CML treated with IM [35].

Over the years, the use of TKIs led the European LeukemiaNet (ELN) to produce and update recommendations for monitoring and assessing the response to these drugs in adults with CP-CML [36,37]. In 2014, modified ELN guidelines were proposed for the management of children and young adults with CP-CML treated with IM [38]. To date, only one study regarding the 2013 ELN recommendations and/or the modified ELN guidelines in childhood CP-CML is available [39]. This Italian cooperative study included 51 pediatric patients managed according to the local guidelines, which provided high-dose IM and cytogenetic and molecular monitoring similarly to that performed in adults. The response rates at 3, 6, and 12 months were higher according to the modified ELN criteria compared with the 2013 ELN recommendations.

In adult CP-CML, the achievement of an early molecular and cytogenetic response to TKIs is considered the major surrogate endpoint predicting outcome in these patients, above all in those treated with high-dose IM or 2GTKI [40–48]. Evaluation of the significance of an early response to TKIs in newly diagnosed CP-CML children has only been reported in a few retrospective studies. In two of these studies, the dose of IM was 260 mg/m²/daily, equal to that used in CP-CML adults (400 mg/daily). Children with BCR-ABL1 IS ≤ 10% at 3 months had higher cytogenetic and molecular responses (MR) (BCR-ABL1 IS ≤ 0.1%) at 12 months and a better progression-free survival compared with those with BCR-ABL1/ABL > 10% [49,50]. Another study showed that the 3-month transcript cutoff levels 10% BCR-ABL1 in children and adolescents with CP-CML treated with IM at a higher dose (340 mg/m²/daily, corresponding to 600 mg/daily) did not predict the outcome [51]. This was due to a greater number of patients who achieved an early response (79.5%), higher than that reported in a comparable number of children treated with lower doses of IM and similar to that observed in adults treated with high-dose IM (600–800 mg/daily) [45–47]. These data suggest that the IM dose is an important factor influencing responses and outcomes in children and adolescents with CP-CML.

4. Which of the TKIs Are Available for Children with CML?

Currently, three TKIs are available for the treatment of CML children, both newly diagnosed in CP and in advanced phases. IM was the first drug to be approved in 2003. More recently, 2GTKI, DASA and NILO, were approved to treat children and adolescents with CML, both newly diagnosed and resistant or intolerant to previous therapy, including IM. Generic preparations of IM and DASA are also available worldwide.

Recently, two studies reported preliminary encouraging data using ponatinib, in compassionate use, in children and adolescents who had previously failed several lines of therapy [52,53]. A phase 1/2 clinical trial of ponatinib for relapsed or refractory pediatric leukemias is ongoing (NCT03934372).

A phase 1/2 pediatric clinical trial for bosutinib is currently under development (NCT04258943).

5. What Is the Treatment of Choice for Pediatric Patients with CP-CML?

The issue of cure versus long-term control is important when discussing treatment for pediatric CP-CML. Prior to the availability of specific TKIs, allogeneic hematopoietic stem cell transplantation (HSCT) was the first-line treatment with proven curative potential for children and adolescents with a suitable HLA-matched donor. Alpha-interferon (IFN), alone or in combination with cytosine-arabioside, was the treatment of choice for children without an available donor [54,55]. In terms of response rate and overall survival (OS), results of IFN in small cohorts of children and adolescents were similar to those reported in adults [55].

The availability of IM and, afterward, 2GTKI revolutionized the first-line treatment in newly diagnosed CP-CML children and adolescents, even in those with an HLA-compatible

family donor. Currently, several therapeutic options even in pediatric CML can offer us the choice of treatment that aims to cure the disease, minimizing toxicity, at least for 6 or 7 decades, as children have a much longer life expectancy than adults. In real life, drug availability, ease of administration, and financial issues are also considered. All the three approved TKIs in children, IM, DASA, and NILO, can be employed as first-line treatment in newly diagnosed CP-CML. Regarding the administration, whereas IM and DASA are given once daily with food, NILO is given twice daily, and food should be avoided 2 h before and 1 h after each dose, so this may be challenging for teenagers. Indeed, adolescence combined with chronic and potentially life-threatening illnesses that require long-term treatment is a high-risk factor for adherence. Regarding the cost, generic IM and DASA are available and are much less expensive than the branded versions and NILO.

In adults, a recent meta-analysis, including seven randomized controlled trials for newly diagnosed CP-CML patients treated with imatinib or later-generation TKIs, demonstrated that second- and third-generation TKIs have proven to be more effective in terms of response and progression of the disease (early MR, transformation to advanced phases), whereas IM has shown to be better in terms of adverse effects [56].

To date, there are no studies that suggest superiority in terms of efficacy and safety, especially long-term side effects of one TKI over another, in newly diagnosed CP-CML children and adolescents. The majority of published clinical trials in this category of patients report data on the treatment of IM, used at different dosage, 260 mg/m²/daily and higher (340 mg/m²/daily) (Table 1). In the first reported study, an open-label multicenter phase II clinical trial, IM was used at a dosage of 340 mg/m²/daily in 51 patients younger than 18 years of age. This dosage of IM, equal to 600 mg/daily in adults, was well-tolerated and showed to be effective in inducing a high rate of cytogenetic and molecular responses in these patients, comparable with that obtained in adults with CP-CML treated with 400 mg/daily [4]. Another cooperative study in which IM was used at a higher dose (340 mg/m²/daily) for a longer period of time (median follow-up: 52 months) in 47 newly diagnosed CP-CML children and adolescents showed better results in terms of response rate (complete cytogenetic response at 6 months: 93%; MR at 12 months: 66%) and outcome. It was also observed that the cumulative rate of cytogenetic and molecular responses increased over time, with a deep molecular response rate of 33% at 12 months [5]. The largest clinical trial included 140 newly diagnosed CP-CML patients under 18 years of age, who received IM at a median average dose of 273 mg/m²/daily for a median follow-up of 25 months [12]. Results in terms of cytogenetic and molecular responses were similar to those obtained in adults treated with IM at a dosage of 400 mg/day [6]. Comparable data had previously been reported on a smaller number of newly diagnosed CP-CML children treated with IM at a dosage of 260 mg/m²/daily [3].

(A phase II study of DASA included children with CML, either resistant and/or intolerant to IM, or in advanced phases [12]. Eighty-four were newly diagnosed CP-CML patients; 51 of them received the tablet drug at the dosage of 60 mg/m²/daily (maximum dose of 100 mg) and 33 were treated with powder for oral suspension at a dosage of 72 mg/m²/daily (maximum dose of 120 mg). Cytogenetic and molecular response rates increased over time, with a MR by 12 and 24 months of therapy of 52 and 70% of patients, respectively, regardless of the drug formulation. These response rates are similar to those reported in a study of pediatric patients treated with a high dose of IM [5] and higher than those reported in children treated with a standard dose of IM [3,4]. DASA was also shown to be well-tolerated without occurrences of pleural or pericardial effusions.

More recently, a phase II study reported results of NILO administered at a dosage of 230 mg/m²/twice a day in 58 children with CP-CML: 33 of them resistant or intolerant to IM and/or DASA and 25 newly diagnosed patients [57]. In this latter category of patients, cytogenetic and MR rates were 64% at 12 months and 68% and 84%, respectively, at 24 months of therapy, similar to that reported in newly diagnosed children treated with DASA or high-dose IM.

Table 1. Results of TKI treatment in larger studies of newly diagnosed CP-CML pediatric patients.

References	Number Patients	Type of TKI	Dose/Daily	CCyR (Time) (%)	Time to CCyR	MMR (Time) (%)	Time to MMR	EFS/PFS/OS Probability	Median Follow-Up
Champagne MA et al., 2011 [4]	51	Imatinib	340 mg/m ²	72%	5.6 mo	27%	NR	3-yrs PFS 72 ± 6.4% 3-yrs OS 92 ± 3.9%	3.8 years
Millot F et al., 2011 [3]	44	Imatinib	260 mg/m ²	12 mo: 61% Overall: 77%	NR	12 mo: 31% Overall: 57%	NR	3-year PFS 98%	31 months
Giona F et al., 2015 [5]	47	Imatinib	340 mg/m ²	6 mo: 93% 12-mo: 96%	6.3 mo	12 mo: MMR 66% 24 mo: MMR 83% Deep MR: 33%	15 months (BCR-ABL1 ≤ 0.01%)	10-yrs PFS: 60% 10-yrs OS: 100%	52 months
Suttorp M et al., 2018 [6]	140	Imatinib	273 mg/m ²	12 mo: 63%	NR	18 mo: 59%	NR	18-mo EFS: 97% 18-mo OS: 100%	25 months
Gore L et al., 2018 [12]	84	Dasatinib	60 mg/m ² (tablet) 72 mg/m ² (PFOS)	6 mo: 55%	5.6 mo	12 mo: MMR 52% 24 mo: MMR 70%	8.9 mo	4-yrs PFR: 94% 4-yrs PFR: 94%	24 months
Hijjiya N et al., 2019 [13]	25	Nilotinib	230 mg/m ² twice daily	12 mo: 64% 24 mo: 84%	5.6 mo	12 mo: 64% 24 mo: 68%	5.6 mo	2-yrs EFS: 91.2%	22 months

TKI: tyrosine kinase inhibitor; CCyR: complete cytogenetic response; MMR: major molecular response; EFS: event-free survival; PFS: progression-free survival; OS: overall survival; PFOS: powder for oral suspension; NR: not reported.

6. What Are the Effective and Optimal Doses of TKIs in Children and Adolescents with CP-CML?

The most common initial dose of IM for pediatric CML-CP ranges 260–340 mg/m²/day based on the results from large pediatric studies. The doses of 260 and 340 mg/m² of IM, used in children and adolescents, are equal to adult doses of 400 and 600 mg, respectively. In children under 4 years of age, the therapeutic dose of IM is difficult to define. Based on the pharmacokinetics of other drugs, infants may require higher doses of IM than older children or adolescents due to an increased metabolism.

The daily dose of DASA in children and adolescents is administered according to weight, with a dose of 40 mg for those weighing 10–20 kg, 60 mg for those weighing 20–30 kg, 70 mg for those weighing 30–45 kg, and 100 mg for those weighing more than 45 kg. DASA is also marketed as a powder for oral suspension, making it usable even in younger children by increasing compliance. The dose of DASA can be increased by 10 mg/day in case of no or unsatisfactory response and can be reduced by 10 mg/day or discontinued for a period not exceeding 3 weeks in case of hematologic toxicity.

In the pediatric population, NILO is administered at a dosage of 230 mg/m² twice daily (up to a maximum single dose of 400 mg), equal to the adult dose of 400 mg twice per day. To date, there are no data available in treating pediatric patients younger than 2 years.

The efficacy of the TKIs in children can be limited by some factors, such as interaction with other drugs and poor adherence, more frequently in adolescents.

The absorption and metabolism of IM may be affected by other concomitant medications.

Swallowing oral tablets or capsules is not easy for children, especially for the younger ones. Liquid formulations of TKIs may be prepared and administered to overcome this hurdle and to improve adherence. Tablets of IM may be dissolved in water or apple juice using 50 mL per 100 mg tablet and immediately drunk. Tablets of DASA can be dissolved over 20 min at room temperature in 30 mL of lemonade, preservative-free apple, or orange juices. After drinking, the residue of the glass can be rinsed with 15 mL of the juice and drunk. Capsules of NILO may be dispersed in 5 mL of grated apple and immediately taken on an empty stomach, and the patient has to wait 1 h before eating.

7. What Are the Potential Side Effects of TKIs on Children?

Short-term toxicity of TKIs is common, but the effects are generally mild to moderate and are manageable. Grade ≥ 2 hematologic toxicity is observed mostly within the first months of treatment. The most frequent extrahematologic side effects of IM include gastrointestinal tract toxicity, arthralgia and myalgia especially in the first month after diagnosis, edema, weight gain, and skin rashes. Myalgia and bone pain have been reported also in children treated with DASA [12]. The most common adverse events observed in children treated with NILO are headaches, pyrexia, increased blood bilirubin, and increased alanine transferase [57].

Currently, most data on long-term and late effects of TKI therapy in pediatric patients concern children and adolescents treated with IM. Delayed growth, dysregulation of bone metabolism and pubertal development, and effects on fertility have been reported during chronic exposure to IM in children, especially in those who started this drug in the prepubertal age [7–11,58,59]. Likewise, various degrees of growth deceleration have been recently reported in CML children treated in prepubertal age with 2GTKI, DASA and NILO [13,60].

The optimal management of children and adolescents suffering from these side effects is still undefined. Attempts have been made in patients treated with IM with persistent deep molecular response (MR4, MR4.5), mostly based on the hypothesis that intermittent target inhibition with TKIs could preserve efficacy and reduce side effects. An improvement of growth and bone metabolism was observed over time in these patients by administering IM at the same daily dose for 3 weeks per month (intermittent IM) [61]. This intermittent schedule has also permitted safely stopping IM in patients with long-lasting deep molecular

response and in improving MR in some patients. Treatment with growth hormone leading to an improvement in growth velocity has been also reported [62].

8. Could TKIs Be Safely Discontinued in Responding Children and Adolescents with CML?

Currently, treatment-free remission (TFR) is a therapeutic goal for the eligible CML adults treated with TKIs. Depth and duration of MR before the discontinuation of TKIs are shown to be major factors associated with relapse-free survival in this category of patients, whatever TKI is utilized. Importantly, TKIs have been effective at inducing a second MMR in adults who resumed the TKI after failed TFR [63–68]. Safely stopping TKIs in responding children and adolescents is a pressing question in this category of patients, facing different long-term side effects with potentially lifelong treatment. To date, only sporadic data on IM discontinuation are available in children. Outcomes of six children who decided by themselves to discontinue IM were suboptimal. All of these children, three of them in molecular response (but for <2 years), had significant rapid increases in the transcript level after cessation of imatinib [69]. Recently, an international prospective study (STOP IMAPED study), which provided IM discontinuation in patients in DMR lasting at least 2 years, reported a molecular relapse in 10 out of 14 enrolled patients within 6 months (median of 3 months) after IM discontinuation. All patients who had a recurrence regained a second molecular response after TKI treatment, demonstrating that temporary IM cessation is safe [70]. An Italian study suggested that IM discontinuation is safely possible in pediatric CML patients with MR4.5-MR5 lasting >24 months and with transcript fluctuations less than 1-molecular log that has been maintained during the intermittent schedule of IM [5,61]. Among 15 patients treated with the intermittent schedule, three who were in prolonged deep MR before the intermittent dosage successfully stopped IM and have remained in TFR for more than 7 years, and eight patients who lost molecular response later regained it on resuming the continuous schedule of the TKI [5,61]. In 2021, a study by the Swedish Chronic Myeloid Leukaemia Registry showed that treatment with TKIs can be safely discontinued in selected CML patients [71].

Currently, considering the importance of this issue and the data available [5,61,70,71], stopping TKIs in children and adolescents is only recommended within clinical trials.

9. How Should Pediatric CML Patients Resistant or Intolerant to TKIs Be Managed?

Compared with adults with CML, there are no additional TKIs currently approved in pediatrics for those patients who present progression of the disease and/or are intolerant to the first- and second-generation TKI. Recently, multicenter retrospective studies reported experience using ponatinib in pediatric patients with Ph+ leukemias [52,53]. In the first study of 21 patients under 21 years of age, nine had CML and had been previously treated with a minimum of one and up to three TKIs. All these patients generally tolerated ponatinib well, with only a few adverse effects, and had promising responses to the disease [52]. In the second study, ponatinib in combination with chemotherapy was effective in inducing MR in three patients with T315I mutation and lymphoid BP [53].

Similar to adults, transplantation is recommended for pediatric patients with the T315I mutation. Currently, allogeneic HSCT is the treatment of choice even for children and adolescents resistant or intolerant to all approved TKIs. Indeed, a survey of 274 North American pediatric oncologists and transplant physicians showed the consensus to recommend allogeneic HSCT in children with CP-CML who previously had failed two TKIs [72].

10. What Is the Role of Allogeneic HSCT in Pediatric CP-CML in the TKI Era?

The role of allogeneic HSCT in pediatric CP-CML has evolved over the years. Until TKIs were available, allogeneic HSCT was considered the optimal curative treatment for children and adolescents with CML. The majority of data on allogeneic HSCT in pediatric CML come from retrospective collaborative studies. The largest clinical study is a report from the EBMT registry, analyzing the outcome of 253 CML children transplanted in first

CP, between January 1985 and December 2001. The OS at 3 years for children who received transplants from sibling donors ($n = 156$) or unrelated donors ($n = 97$) was 75% and 65%, respectively. The transplant-related mortality (TRM) was as high as 20% and 31% in patients who received transplants from sibling donors and in those from unrelated donors, respectively. The most frequent cause of death was graft-versus-host disease (GVHD) [73]. Subsequent studies reported conflicting results in terms of the outcome of HSCT in pediatric CML patients transplanted in the first CP [74–77]. In 1995, a prospective phase I study began that aimed at transplanting children in the first CML-CP from a matched family donor within 6 months from diagnosis or from an unrelated donor within 12 months, initially treated with hydroxyurea \pm IFN and/or IM. It was stopped in 2004 due to poor patient accrual once IM had been fully licensed. The 5-year event-free survival (EFS) was $87 \pm 11\%$ in the group grafted from HLA-identical family donors ($n = 41$) and $52 \pm 9\%$ and $45 \pm 16\%$ in patients transplanted from an HLA-matched donor ($n = 71$) and in those grafted from an HLA-mismatched unrelated donor ($n = 36$), respectively [76].

The current use of IM and, afterward, the availability of 2GTKI have progressively influenced the choice of first-line treatment in newly diagnosed CP-CML children and adolescents. The high short-term responses to TKI therapy associated with few early toxicities have led the majority of pediatric oncologists and/or hematologists to replace transplantation with target therapy in this category of patients in spite of the development of safer transplant procedures, less expensive than the targeted therapy. Indeed, a TRM of 0% was reported in a small group of pediatric patients with first CP-CML early grafted after a short period of treatment with a TKI [5]. Moreover, the US Patient Survival Report from the Health Resources and Services Administration (http://bloodcell.transplant.hrsa.gov/research/transplant_data/us_tx_data/survival_data/survival.aspx, (accessed on 1 January 2022)) reported a 100-day TRM of 0 and 5% for related and unrelated donors, respectively, in patients under 21 years of age, transplanted in the first CP-CML.

Regarding the price of the “cure” of an adolescent with CP-CML, in the US, the estimated long-term financial cost for the TKI treatment is USD 1.9 million, compared with about USD 250,000 for allogeneic HSCT. In countries with limited resources, allogeneic HSCT could be considered for pediatric patients, as the long-term OS is similar for those allografted or given a TKI. The cost of a transplant from a matched family donor is comparable with the cost of 180 days of branded TKI treatment [78]. Another retrospective study including CP-CML children, who were allografted from a matched family donor from 2007 to 2017, reported the 5-year probability of OS at 97.4%, similar to that of patients treated with TKIs, with a TRM at 100 days and at 1-year post-transplant of 0% [79]. Over the last few years, a treatment algorithm for newly diagnosed CML patients based on drug availability in an environment with limited resources was proposed [80].

11. How Can the Advanced Phases Be Treated?

Data of children and adolescents with advanced phases of CML, *de novo* or occurring under treatment, are very limited due to the rarity of this condition. Nevertheless, the use of TKIs, at higher doses than those employed in the CP-CML, alone or in combination with chemotherapy, has been reported to dramatically improve prognosis in pediatric CML in advanced phases as well. The recommended pediatric doses of IM for CML-AP and CML-BC are $400 \text{ mg/m}^2/\text{day}$ (maximum dose of 600 mg) and 500 mg/m^2 (maximum dose of 800 mg), respectively. DASA is recommended at a dose of $80 \text{ mg/m}^2/\text{day}$ for children with CML-AP/BP.

The largest data available on pediatric CML patients in advanced phases are from the “International Registry of Chronic Myeloid Leukemia in Children and Adolescents” and include 36 children with *de novo* AP-CML ($n = 19$) or *de novo* BP-CML ($n = 17$) [24]. All these patients were initially treated with TKIs, combined or not with chemotherapy, and 33 of them (92%) achieved a complete hematologic response (CHR). Out of 17 AP-CML patients who achieved CHR, 15 were treated with IM alone, and 6 were submitted to allogeneic HSCT. Out of 17 BP-CML patients, 7 were treated with IM alone, whereas

10 patients were treated with chemotherapy combined with IM or 2GTKI. Sixteen (94%) obtained CHR, and 11 were submitted to allogeneic HSCT. Five-year OS probabilities were 94% (95% CI: 66–99%) and 74% (95% CI: 44–89%) for AP-CML and BC-CML patients, respectively. Although the number of pediatric patients in this study is small, some considerations can be made. In the TKI era, the OS of children and adolescents with a diagnosis of CML in the advanced phase is higher than that reported in the same category of adults [81–83]. Moreover, the outcome of pediatric patients with AP-CML and BP-CML at diagnosis seems to be favorable even without HSCT.

Data in CML children and adolescents who developed an advanced phase under treatment or after allogeneic HSCT are very limited. In our personal experience, before the advent of TKIs, the prognosis of children and adolescents with an advanced phase during treatment was poor. Afterward, children and adolescents who developed AP or BP during treatment were successfully treated with TKIs, alone or in combination with chemotherapy, followed by allogeneic HSCT. Recently, a retrospective study reported the outcome of eight pediatric patients with CML who developed an advanced phase during TKI treatment, or after transplantation (four patients), and were treated with ponatinib at a median dose of 21 mg/m²/daily, alone (four patients) or in combination with chemotherapy. No extrahematologic toxicity related to ponatinib was observed. MR was observed in five patients, four of them treated with combinations of chemotherapy and ponatinib. No response was recorded in three patients receiving ponatinib alone. Three out of five responding children underwent allogeneic HSCT; unfortunately, all of them died of disease progression [52].

12. Conclusions

Recent studies in the molecular biology of pediatric CML are beginning to elucidate the differences between childhood and adult CML, which could explain the clinical differences in disease presentation and outcome. Despite the fact that treatment with TKIs has considerably improved prognosis, many issues in the treatment of children and adolescents with CML still remain unanswered. First of all, it is important to define the TKI of choice as first-line treatment in CP-CML children and adolescents, considering the long-term side effects, especially with 2GTKI, which are still poorly studied in this category of patients. Second, the optimal treatment of pediatric patients with CML, in an advanced phase de novo, or during treatment, remains to be determined. Moreover, excluding patients with T315I mutation, the role of allogeneic HSCT has to be well-defined in pediatric patients with CML both in CP and in advanced phases. Finally, collaborative clinical trials held within international cooperative pediatric groups (e.g., COG and I-BFM groups) could allow the safe suspension of target treatment in CP-CML children and adolescents who have achieved a deep MR.

Author Contributions: Conceptualization, methodology, and writing original draft preparation F.G.; writing revue and editing, S.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Howlader, N.; Noone, A.M.; Krapcho, M.; Miller, D.; Brest, A.; Yu, M.; Ruhl, J.; Tatalovich, Z.; Mariotto, A.; Lewis, D.R.; et al. *SEER Cancer Statistics Review, 1975–2017*; National Cancer Institute: Bethesda, MD, USA, 2020.
2. Andolina, J.R.; Neudorf, S.M.; Corey, S.J. How I treat childhood CML. *Blood* **2012**, *119*, 1821–1830. [[CrossRef](#)] [[PubMed](#)]

3. Millot, F.; Baruchel, A.; Guilhot, J.; Petit, A.; Leblanc, T.; Bertrand, Y.; Mazingue, F.; Lutz, P.; Vérité, C.; Berthou, C.; et al. Imatinib Is effective in children with previously untreated chronic myelogenous leukemia in early chronic phase: Results of the French national phase IV trial. *J. Clin. Oncol.* **2011**, *29*, 2827–2832. [[CrossRef](#)] [[PubMed](#)]
4. Champagne, M.A.; Fu, C.H.; Chang, M.; Chen, H.; Gerbing, R.B.; Alonzo, T.A.; Cooley, L.; Heerema, N.A.; Oehler, V.; Wood, C.; et al. Higher dose imatinib for children with de novo chronic phase chronic myelogenous leukemia: A report from the Children's Oncology Group. *Pediatr. Blood Cancer* **2011**, *57*, 56–62. [[CrossRef](#)] [[PubMed](#)]
5. Giona, F.; Putti, M.C.; Micalizzi, C.; Menna, G.; Moleti, M.L.; Santoro, N.; Iaria, G.; Ladogana, S.; Burnelli, R.; Consarino, C.; et al. Long-term results of high-dose imatinib in children and adolescents with chronic myeloid leukaemia in chronic phase: The Italian experience. *Br. J. Haematol.* **2015**, *170*, 398–407. [[CrossRef](#)]
6. Suttorp, M.; Schulze, P.; Glauche, I.; Göhring, G.; von Neuhoff, N.; Metzler, M.; Sedlacek, P.; de Bont, E.S.J.M.; Balduzzi, A.; Lausen, B.; et al. Front-line imatinib treatment in children and adolescents with chronic myeloid leukemia: Results from a phase III trial. *Leukemia* **2018**, *32*, 1657–1669. [[CrossRef](#)]
7. Shima, H.; Tokuyama, M.; Tanizawa, A.; Tono, C.; Hamamoto, K.; Muramatsu, H.; Watanabe, A.; Hotta, N.; Ito, M.; Kurosawa, H.; et al. Distinct impact of imatinib on growth at prepubertal and pubertal ages of children with chronic myeloid leukemia. *J. Pediatr.* **2011**, *159*, 676–681. [[CrossRef](#)]
8. Bansal, D.; Shava, U.; Varma, N.; Trehan, A.; Marwaha, R.K. Imatinib has adverse effect on growth in children with chronic myeloid leukemia. *Pediatr. Blood Cancer* **2012**, *59*, 481–484. [[CrossRef](#)]
9. Giona, F.; Mariani, S.; Gnassi, L.; Moleti, M.L.; Rea, M.; De Vellis, A.; Marzella, D.; Testi, A.M.; Foà, R. Bone metabolism, growth rate and pubertal development in children with chronic myeloid leukemia treated with imatinib during puberty. *Haematologica* **2013**, *98*, e25. [[CrossRef](#)]
10. Millot, F.; Guilhot, J.; Baruchel, A.; Petit, A.; Leblanc, T.; Bertrand, Y.; Mazingue, F.; Lutz, P.; Vérité, C.; Berthou, C.; et al. Growth deceleration in children treated with imatinib for chronic myeloid leukaemia. *Eur. J. Cancer* **2014**, *50*, 3206–3211. [[CrossRef](#)]
11. Samis, J.; Lee, P.; Zimmerman, D.; Arceci, R.J.; Suttorp, M.; Hijiya, N. Recognizing endo- crinopathies associated with tyrosine kinase inhibitor therapy in children with chronic my- elogenous leukemia. *Pediatr. Blood Cancer* **2016**, *63*, 1332–1338. [[CrossRef](#)]
12. Gore, L.; Kearns, P.R.; de Martino, M.L.; De Souza, C.A.; Bertrand, Y.; Hijiya, N.; Stork, L.C.; Chung, N.G.; Cardos, R.C.; Saikia, T.; et al. Dasatinib in Pediatric Patients With Chronic Myeloid Leukemia in Chronic Phase: Results From a Phase II Trial. *J. Clin. Oncol.* **2018**, *36*, 1330–1338. [[CrossRef](#)] [[PubMed](#)]
13. Hijiya, N.; Maschan, A.; Rizzari, C.; Shimada, H.; Dufour, C.; Goto, H.; Kang, H.J.; Guinipero, T.; Karakas, Z.; Bautista, F.; et al. A phase 2 study of nilotinib in pediatric patients with CML: Long-term update on growth retardation and safety. *Blood Adv.* **2021**, *5*, 2925–2934. [[CrossRef](#)] [[PubMed](#)]
14. Hijiya, N.; Millot, F.; Suttorp, M. Chronic myeloid leukemia in children: Clinical findings, management, and unanswered questions. *Pediatr. Clin. N. Am.* **2015**, *62*, 107–119. [[CrossRef](#)] [[PubMed](#)]
15. Millot, F.; Traore, P.; Guilhot, J.; Nelken, B.; Leblanc, T.; Leverger, G.; Plantaz, D.; Bertrand, Y.; Bordigoni, P.; Guilhot, F. Clinical and biological features at diagnosis in 40 children with chronic myeloid leukemia. *Pediatrics* **2005**, *116*, 140–143. [[CrossRef](#)]
16. Millot, F.; Suttorp, M.; Guilhot, J.; Sedlacek, P.; De Bont, E.S.; Li, C.K.; Kalwak, K.; Lausen, B.; Culic, S.; Dresse, M.F.; et al. The International Registry for Chronic Myeloid Leukemia (CML) in Children and Adolescents (I-CML-Ped-Study): Objectives and preliminary results. *Blood* **2012**, *120*, 3741. [[CrossRef](#)]
17. Kalmanti, L.; Saussele, S.; Lauseker, M.; Proetel, U.; Müller, M.C.; Hanfstein, B.; Schreiber, A.; Fabarius, A.; Pfirrmann, M.; Schnittger, S.; et al. Younger patients with chronic myeloid leukemia do well in spite of poor prognostic indicators: Results from the randomized CML study IV. *Ann. Hematol.* **2014**, *93*, 71–80. [[CrossRef](#)]
18. Krumbholz, M.; Karl, M.; Tauer, J.T.; Thiede, C.; Rascher, W.; Suttorp, M.; Metzler, M. Genomic BCR-ABL1 breakpoints in pediatric chronic myeloid leukemia. *Genes Chromosomes Cancer* **2012**, *51*, 1045–1053. [[CrossRef](#)]
19. Meissner, R.V.; Dias, P.M.; Covas, D.T.; Job, F.; Leite, M.; Nardi, N.B. A polymorphism in exon b2 of the major breakpoint cluster region (M-bcr) identified in chronic myeloid leukaemia patients. *Br. J. Haematol.* **1998**, *103*, 224–226. [[CrossRef](#)]
20. Branford, S.; Rudzki, Z.; Walsh, S.; Grigg, A.; Arthur, C.; Taylor, K.; Herrmann, R.; Lynch, K.P.; Hughes, T.P. High frequency of point mutations clustered within the adenosine triphosphate-binding region of BCR/ABL in patients with chronic myeloid leukemia or Ph-positive acute lymphoblastic leukemia who develop imatinib (STI571) resistance. *Blood* **2002**, *99*, 3472–3475. [[CrossRef](#)]
21. Schmidt, M.; Rinke, J.; Schäfer, V.; Schnittger, S.; Kohlmann, A.; Obstfelder, E.; Kunert, C.; Ziermann, J.; Winkelmann, N.; Eigendorff, E.; et al. Molecular-defined clonal evolution in patients with chronic myeloid leukemia independent of the BCR-ABL status. *Leukemia* **2014**, *28*, 2292–2299. [[CrossRef](#)]
22. Ernst, T.; Busch, M.; Rinke, J.; Ernst, J.; Haferlach, C.; Beck, J.F.; Hochhaus, A.; Gruhn, B. Frequent ASXL1 mutations in children and young adults with chronic myeloid leukemia. *Leukemia* **2018**, *32*, 2046–2049. [[CrossRef](#)] [[PubMed](#)]
23. Youn, M.; Smith, S.M.; Lee, A.G.; Chae, H.D.; Spiteri, E.; Erdmann, J.; Galperin, I.; Jones, L.M.; Donato, M.; Abidi, P.; et al. Comparison of the Transcriptomic Signatures in Pediatric and Adult CML. *Cancers* **2021**, *13*, 6263. [[CrossRef](#)] [[PubMed](#)]
24. Radivoyevitch, T.; Hlatky, L.; Landaw, J.; Sachs, R.K. Quantitative modeling of chronic myeloid leukemia: Insights from radiobiology. *Blood* **2012**, *119*, 4363–4371. [[CrossRef](#)] [[PubMed](#)]
25. Millot, F.; Maledon, N.; Guilhot, J.; Güneş, A.M.; Kalwak, K.; Suttorp, M. Favourable outcome of de novo advanced phases of childhood chronic myeloid leukaemia. *Eur. J. Cancer* **2019**, *115*, 17–23. [[CrossRef](#)]

26. Adler, R.; Viehmann, S.; Kuhlisch, E.; Martiniak, Y.; Röttgers, S.; Harbott, J.; Suttorp, M. Correlation of BCR/ABL transcript variants with patients' characteristics in childhood chronic myeloid leukaemia. *Eur. J. Haematol.* **2009**, *82*, 112–118. [[CrossRef](#)]
27. Castagnetti, M.; Sainati, L.; Giona, F.; Varotto, S.; Carli, M.; Rigamonti, W. Conservative management of priapism secondary to leukemia. *Pediatr. Blood Cancer* **2008**, *51*, 420–423. [[CrossRef](#)]
28. Kurosawa, H.; Tanizawa, A.; Tono, C.; Watanabe, A.; Shima, H.; Ito, M.; Yuza, Y.; Hotta, N.; Muramatsu, H.; Okada, M.; et al. Leukostasis in Children and Adolescents with Chronic Myeloid Leukemia: Japanese Pediatric Leukemia/Lymphoma Study Group. *Pediatr. Blood Cancer* **2016**, *63*, 406–411. [[CrossRef](#)]
29. Sokal, J.E.; Cox, E.B.; Baccarani, M.; Tura, S.; Gomez, G.A.; Robertson, J.E.; Tso, C.Y.; Braun, T.J.; Clarkson, B.D.; Cervantes, F. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. *Blood* **1984**, *63*, 789–799. [[CrossRef](#)]
30. Hasford, J.; Pffirmann, M.; Hehlmann, R.; Allan, N.C.; Baccarani, M.; Kluin-Nelemans, J.C.; Alimena, G.; Steegmann, J.L.; Ansari, H.J. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. *Natl. Cancer Inst.* **1998**, *90*, 850–858. [[CrossRef](#)]
31. Hasford, J.; Baccarani, M.; Hoffmann, V.; Guilhot, J.; Saussele, S.; Rosti, G.; Guilhot, F.; Porkka, K.; Ossenkoppele, G.; Lindoerfer, D.; et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: The EUTOS score. *Blood* **2011**, *118*, 686–692. [[CrossRef](#)]
32. Gurrea Salas, D.; Glauche, I.; Tauer, J.T.; Thiede, C.; Suttorp, M. Can prognostic scoring systems for chronic myeloid leukemia as established in adults be applied to pediatric patients? *Ann. Hematol.* **2015**, *94*, 1363–1371. [[CrossRef](#)] [[PubMed](#)]
33. Pffirmann, M.; Baccarani, M.; Saussele, S.; Guilhot, J.; Cervantes, F.; Ossenkoppele, G.; Hoffmann, V.S.; Castagnetti, F.; Hasford, J.; Hehlmann, R.; et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. *Leukemia* **2016**, *30*, 48–56. [[CrossRef](#)] [[PubMed](#)]
34. Geelen, I.G.P.; Sandin, F.; Thielen, N.; Janssen, J.J.W.M.; Hoogendoorn, M.; Visser, O.; Cornelissen, J.J.; Hoglund, M.; Westerweel, P.E. Validation of the EUTOS long-term survival score in a recent independent cohort of "real world" CML patients. *Leukemia* **2018**, *32*, 2299–2303. [[CrossRef](#)] [[PubMed](#)]
35. Millot, F.; Guilhot, J.; Suttorp, M.; Güneş, A.M.; Sedlacek, P.; De Bont, E.; Li, C.K.; Kalwak, K.; Lausen, B.; Culic, S.; et al. Prognostic discrimination based on the EUTOS long-term survival score within the International Registry for Chronic Myeloid Leukemia in children and adolescents. *Haematologica* **2017**, *102*, 1704–1708. [[CrossRef](#)] [[PubMed](#)]
36. Baccarani, M.; Saglio, G.; Goldman, J.; Hochhaus, A.; Simonsson, B.; Appelbaum, F.; Apperley, J.; Cervantes, F.; Cortes, J.; Deininger, M.; et al. Evolving concepts in the management of chronic myeloid leukemia: Recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood* **2006**, *108*, 1809–2039. [[CrossRef](#)]
37. Baccarani, M.; Castagnetti, F.; Gugliotta, G.; Rosti, G. A review of the European LeukemiaNet recommendations for the management of CML. *Ann. Hematol.* **2015**, *94* (Suppl. S2), S141–S147. [[CrossRef](#)] [[PubMed](#)]
38. de la Fuente, J.; Baruchel, A.; Biondi, A.; de Bont, E.; Dresse, M.F.; Suttorp, M.; Millot, F.; International BFM Group (iBFM) Study Group Chronic Myeloid Leukaemia Committee. Managing children with chronic myeloid leukaemia (CML): Recommendations for the management of CML in children and young people up to the age of 18 years. *Br. J. Haematol.* **2014**, *167*, 33–47. [[CrossRef](#)]
39. Giona, F.; Saglio, G.; Santopietro, M.; Menna, G.; Putti, M.C.; Micalizzi, C.; Iaria, G.; Santoro, N.; Ladogana, S.; Mura, R.; et al. Managing Children and Adolescents with Chronic Myeloid Leukemia Treated with High-Dose Imatinib. The Italian Experience. EHA. In Proceedings of the 21st Congress of the European Hematology Association Copenhagen, The Italian Experience. EHA. Copenhagen, Denmark, 9–12 June 2016; p. 236.
40. Neelakantan, P.; Gerrard, G.; Lucas, C.; Milojkovic, D.; May, P.; Wang, L.; Paliompeis, C.; Bua, M.; Reid, A.; Rezvani, K.; et al. Combining BCR-ABL1 transcript levels at 3 and 6 months in chronic myeloid leukemia: Implications for early intervention strategies. *Blood* **2013**, *121*, 2739–2742. [[CrossRef](#)]
41. Hanfstein, B.; Müller, M.C.; Hehlmann, R.; Erben, P.; Lauseker, M.; Fabarius, A.; Schnittger, S.; Haferlach, C.; Göhring, G.; Proetel, U.; et al. Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). *Leukemia* **2012**, *26*, 2096–2102. [[CrossRef](#)]
42. Hughes, T.P.; Saglio, G.; Kantarjian, H.M.; Guilhot, F.; Niederwieser, D.; Rosti, G.; Nakaseko, C.; De Souza, C.A.; Kalaycio, M.E.; Meier, S.; et al. Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. *Blood* **2014**, *123*, 1353–1360. [[CrossRef](#)]
43. Branford, S.; Yeung, D.T.; Parker, W.T.; Roberts, N.D.; Purins, L.; Braley, J.A.; Altamura, H.K.; Yeoman, A.L.; Georgievski, J.; Jamison, B.A.; et al. Prognosis for patients with CML and >10% BCR-ABL1 after 3 months of imatinib depends on the rate of BCR-ABL1 decline. *Blood* **2014**, *124*, 511–518. [[CrossRef](#)] [[PubMed](#)]
44. Hanfstein, B.; Shlyakhto, V.; Lauseker, M.; Hehlmann, R.; Saussele, S.; Dietz, C.; Erben, P.; Fabarius, A.; Proetel, U.; Schnittger, S.; et al. Velocity of early BCR-ABL transcript elimination as an optimized predictor of outcome in chronic myeloid leukemia (CML) patients in chronic phase on treatment with imatinib. *Leukemia* **2014**, *28*, 1988–1992. [[CrossRef](#)] [[PubMed](#)]
45. Deininger, M.W.; Kopecky, K.J.; Radich, J.P.; Kamel-Reid, S.; Stock, W.; Paietta, E.; Emanuel, P.D.; Tallman, M.; Wadleigh, M.; Larson, R.A.; et al. Imatinib 800 mg daily induces deeper molecular responses than imatinib 400 mg daily: Results of SWOG S0325, an intergroup randomized PHASE II trial in newly diagnosed chronic phase chronic myeloid leukaemia. *Br. J. Haematol.* **2014**, *164*, 223–232. [[CrossRef](#)] [[PubMed](#)]

46. Cortes, J.E.; Baccarani, M.; Guilhot, F.; Druker, B.J.; Branford, S.; Kim, D.W.; Pane, F.; Pasquini, R.; Goldberg, S.L.; Kalaycio, M.; et al. Phase III, randomized, open-label study of daily imatinib mesylate 400 mg versus 800 mg in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase using molecular end points: Tyrosine kinase inhibitor optimization and selectivity study. *J. Clin. Oncol.* **2010**, *28*, 424–430.
47. Hehlmann, R.; Lauseker, M.; Jung-Munkwitz, S.; Leitner, A.; Müller, M.C.; Pletsch, N.; Proetel, U.; Haferlach, C.; Schlegelberger, B.; Balleisen, L.; et al. Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon- α in newly diagnosed chronic myeloid leukemia. *J. Clin. Oncol.* **2011**, *29*, 1634–1642. [[CrossRef](#)]
48. Jain, P.; Kantarjian, H.; Nazha, A.; O'Brien, S.; Jabbour, E.; Romo, C.G.; Pierce, S.; Cardenas-Turanzas, M.; Verstovsek, S.; Borthakur, G.; et al. Early responses predict better outcomes in patients with newly diagnosed chronic myeloid leukemia: Results with four tyrosine kinase inhibitor modalities. *Blood* **2013**, *121*, 4867–4874. [[CrossRef](#)]
49. Millot, F.; Guilhot, J.; Baruchel, A.; Petit, A.; Bertrand, Y.; Mazingue, F.; Lutz, P.; Vérité, C.; Berthou, C.; Galambrun, C.; et al. Impact of early molecular response in children with chronic myeloid leukemia treated in the French Glivec phase 4 study. *Blood* **2014**, *124*, 2408–2410. [[CrossRef](#)]
50. Shao, H.; Zeng, Z.; Cen, J.; Zhang, J.; Bai, S.; Wu, C.; Gong, Y.; Wang, Y.; Qiu, H.; Chen, S.; et al. The impact of early molecular response in children and adolescents with chronic myeloid leukemia treated with imatinib: A single-center study from China. *Leuk Lymphoma* **2018**, *59*, 2152–2158. [[CrossRef](#)]
51. Giona, F.; Saglio, G.; Santopietro, M.; Menna, G.; Putti, M.C.; Micalizzi, C.; Iaria, G.; Santoro, N.; Ladogana, S.; Mura, R.; et al. Early response does not predict outcome in children and adolescents with chronic myeloid leukaemia treated with high-dose imatinib. *Br. J. Haematol.* **2016**, *180*, 895–898. [[CrossRef](#)]
52. Rossoff, J.; Huynh, V.; Rau, R.E.; Macy, M.E.; Sulis, M.L.; Schultz, K.R.; Burke, M.J.; Athale, U.; O'Brien, M.M.; Gregory, J.J., Jr.; et al. Experience with ponatinib in paediatric patients with leukaemia. *Br. J. Haematol.* **2020**, *189*, 363–368. [[CrossRef](#)]
53. Millot, F.; Suttorp, M.; Versluys, A.B.; Kalwak, K.; Nelken, B.; Ducassou, S.; Bertrand, Y.; Baruchel, A. ponatinib in childhood Philadelphia chromosome-positive leukemias: An international registry of childhood Chronic Myeloid Leukaemia Study. *Eur. J. Cancer* **2020**, *136*, 107–112. [[CrossRef](#)] [[PubMed](#)]
54. Millot, F.; Brice, P.; Philippe, N.; Thyss, A.; Demeoq, F.; Wetterwald, M.; Boccara, J.F.; Vilque, J.P.; Guyotat, D.; Guilhot, J.; et al. Alpha-interferon in combination with cytarabine in children with Philadelphia chromosome-positive chronic myeloid leukemia. *J. Pediatr. Hematol. Oncol.* **2002**, *24*, 18–22. [[CrossRef](#)] [[PubMed](#)]
55. Giona, F.; Moleti, M.L.; Giudice, I.D.; Testi, A.M.; Diverio, D.; De Cuia, M.R.; Mandelli, F.; Foa, R. Long-term Follow-up of Philadelphia chromosome-positive (Ph) chronic myeloid leukaemia (CML) in children and adolescents managed at a single institution over a 20-year period. *Br. J. Haematol.* **2005**, *130*, 970–972. [[CrossRef](#)] [[PubMed](#)]
56. Vener, C.; Banzi, R.; Ambrogio, F.; Ferrero, A.; Saglio, G.; Pravettoni, G.; Sant, M. First-line imatinib vs second- and third-generation TKIs for chronic-phase CML: A systematic review and meta-analysis. *Blood Adv.* **2020**, *4*, 2723–2735. [[CrossRef](#)] [[PubMed](#)]
57. Hijiya, N.; Maschan, A.; Rizzari, C.; Shimada, H.; Dufour, C.; Goto, H.; Kang, H.J.; Guinipero, T.; Karakas, T.; Bautista, F.; et al. Phase 2 study of nilotinib in pediatric patients with Philadelphia chromosome-positive chronic myeloid leukemia. *Blood* **2019**, *134*, 2036–2045. [[CrossRef](#)]
58. Mariani, S.; Giona, F.; Basciani, S.; Brama, M.; Gnessi, L. Low bone density and decreased inhibin-B/FSH ratio in a boy treated with imatinib during puberty. *Lancet* **2008**, *372*, 111–112. [[CrossRef](#)]
59. Tauer, J.T.; Nowasz, C.; Sedlacek, P.; de Bont, E.S.J.M.; Aleinikova, O.V.; Suttorp, M. Impairment of longitudinal growth by tyrosine kinase inhibitor (TKI) treatment—Data from a large pediatric cohort with chronic myeloid leukemia (CML). *Blood* **2014**, *124*, 522. [[CrossRef](#)]
60. Patterson, B.; Samis, J.; Gore, L.; Zwaan, C.M.; Sacchi, M.; Sy, O.; Hijiya, N. Growth rate and endocrine effects of dasatinib therapy observed in a retrospective analysis of a phase 2 clinical trial for pediatric patients with chronic myeloid leukemia in chronic phase (CML-CP). *HemaSphere* **2019**, *3*, 161. [[CrossRef](#)]
61. Giona, F.; Malaspina, F.; Putti, M.C.; Ladogana, S.; Mura, R.; Burnelli, R.; Vacca, N.; Rizzo, L.; Bianchi, S.; Moleti, M.L.; et al. Results and outcome of intermittent imatinib (ON/OFF schedule) in children and adolescents with chronic myeloid leukaemia. *Br. J. Haematol.* **2020**, *188*, e101–e105. [[CrossRef](#)]
62. Walia, R.; Aggarwal, A.; Bhansali, A.; Aggarwal, A.; Varma, N.; Sachdeva, N.; Khandelwal, N.; Bansal, D. Acquired neurosecretory defect in growth hormone secretion due to Imatinib mesylate and the efficacy of growth hormone therapy in children with chronic myeloid leukemia. *Pediatr. Hematol. Oncol.* **2020**, *37*, 99–108. [[CrossRef](#)]
63. Rousselot, P.; Charbonnier, A.; Cony-Makhoul, P.; Agape, P.; Nicolini, F.E.; Varet, B.; Gardembas, M.; Etienne, G.; Rea, D.; Roy, L.; et al. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. *J. Clin. Oncol.* **2014**, *32*, 424–430. [[CrossRef](#)] [[PubMed](#)]
64. Etienne, G.; Guilhot, J.; Rea, D.; Rigal-Huguet, F.; Nicolini, F.; Charbonnier, A.; Guerci-Bresler, A.; Legros, L.; Varet, B.; Gardembas, M.; et al. Long-term follow-up of the french stop imatinib (STIM1) study in patients with chronic myeloid leukemia. *J. Clin. Oncol.* **2017**, *35*, 298–305. [[CrossRef](#)] [[PubMed](#)]
65. Rea, D.; Nicolini, F.E.; Tulliez, M.; Guilhot, F.; Guilhot, J.; Guerci-Bresler, A.; Gardembas, M.; Coiteux, V.; Guillerm, G.; Legros, L.; et al. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: Interim analysis of the STOP 2G-TKI study. *Blood* **2017**, *129*, 846–854. [[CrossRef](#)] [[PubMed](#)]

66. Hochhaus, A.; Masszi, T.; Giles, F.J.; Radich, J.P.; Ross, D.M.; Gomez Casares, M.T.; Hellmann, A.; Stentoft, J.; Conneally, E.; García-Gutiérrez, V.; et al. Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: Results from the ENESTfreedom study. *Leukemia* **2017**, *31*, 1525–1531. [[CrossRef](#)] [[PubMed](#)]
67. Saussele, S.; Richter, J.; Guilhot, J.; Gruber, F.X.; Hjorth-Hansen, H.; Almeida, A.; Janssen, J.J.W.M.; Mayer, P.J.; Koskenvesa, P.; Panayiotidis, P.; et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): A prespecified interim analysis of a prospective, multicentre, nonrandomised, trial. *Lancet Oncol.* **2018**, *19*, 747–757. [[CrossRef](#)]
68. Hochhaus, A.; Baccarani, M.; Silver, R.T.; Schiffer, C.; Apperley, J.F.; Cervantes, F.; Clark, R.E.; Cortes, J.E.; Deininger, M.W.; Guilhot, F.; et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia* **2020**, *34*, 966–984. [[CrossRef](#)]
69. Millot, F.; Claviez, A.; Leverger, G.; Corbaciglu, S.; Groll, A.H.; Suttorp, M. Imatinib cessation in children and adolescents with chronic myeloid leukemia in chronic phase. *Pediatr. Blood Cancer* **2014**, *61*, 355–357. [[CrossRef](#)]
70. de Bruijn, C.M.A.; Millot, F.; Suttorp, M.; Borisevich, M.; Brons, P.; Lausen, B.; de Bont, E.S.J.M. Discontinuation of imatinib in children with chronic myeloid leukaemia in sustained deep molecular remission: Results of the STOP IMAPED study. *Br. J. Haematol.* **2019**, *185*, 718–724. [[CrossRef](#)]
71. Flygt, H.; Sandin, F.; Dahlén, T.; Dremaine, A.; Lübking, A.; Markevärn, B.; Myhr-Eriksson, C.; Olsson, K.; Olsson-Strömberg, U.; Sjölander, A.; et al. Successful tyrosine kinase inhibitor discontinuation outside clinical trials—Data from the population-based Swedish chronic myeloid leukaemia registry. *Br. J. Haematol.* **2021**, *193*, 915–921. [[CrossRef](#)]
72. Andolina, J.R.; Burke, M.J.; Hijiya, N.; Chaudhury, S.; Schultz, K.R.; Roth, M.E. Practice patterns of physician treatment for pediatric chronic myelogenous leukemia. *Biol. Blood Marrow Transpl.* **2019**, *25*, 321–327. [[CrossRef](#)]
73. Cwynarski, K.; Roberts, I.A.; Iacobelli, S.; Van Biezen, A.; Brand, R.; Devergie, A.; Vossen, J.M.; Aljurf, M.; Arcese, W.; Locatelli, F.; et al. Stem cell transplantation for chronic myeloid leukemia in children. *Blood* **2003**, *102*, 1224–1231. [[CrossRef](#)] [[PubMed](#)]
74. Suttorp, M.; Yaniv, I.; Schultz, K.R. Controversies in the treatment of CML in children and adolescents: TKI versus BMT? *Biol. Blood Marrow Transpl.* **2011**, *17* (Suppl. S1), S115–S122. [[CrossRef](#)] [[PubMed](#)]
75. Muramatsu, H.; Kojima, S.; Yoshimi, A.; Atsuta, Y.; Kato, K.; Nagatoshi, Y.; Inoue, M.; Koike, K.; Kawase, T.; Ito, M.; et al. Outcome of 125 children with chronic myelogenous leukemia who received transplants from unrelated donors: The Japan Marrow Donor Program. *Biol. Blood Marrow Transpl.* **2010**, *16*, 231–238. [[CrossRef](#)] [[PubMed](#)]
76. Chaudhury, S.; Sparapani, R.; Hu, Z.H.; Nishihori, T.; Abdel-Azim, H.; Malone, A.; Olsson, R.; Hamadani, M.; Daly, A.; Bacher, U.; et al. Outcomes of Allogeneic Hematopoietic Cell Transplantation in Children and Young Adults with Chronic Myeloid Leukemia: A CIBMTR Cohort Analysis. *Biol. Blood Marrow Transpl.* **2016**, *22*, 1056–1064. [[CrossRef](#)] [[PubMed](#)]
77. Suttorp, M.; Claviez, A.; Bader, P.; Peters, C.; Gadner, H.; Ebell, W.; Dilloo, D.; Kremens, B.; Kabisch, H.; Führer, M.; et al. Allogeneic stem cell transplantation for pediatric and adolescent patients with CML: Results from the prospective trial CML-paed I. *Klin. Padiatr.* **2009**, *221*, 351–357. [[CrossRef](#)] [[PubMed](#)]
78. Ruiz-Argüelles, G.J.; Tarin-Arzaga, L.C.; Gonzalez-Carrillo, M.L.; Gutierrez-Riveroll, K.I.; Rangel-Malo, R.; Gutiérrez-Aguirre, C.H.; Cantú-Rodríguez, O.G.; Gómez-Almaguer, D.; Giralt, S. Therapeutic choices in patients with Ph-positive CML living in Mexico in the tyrosine kinase inhibitor era: SCT or TKIs? *Bone Marrow Transpl.* **2008**, *42*, 23–28. [[CrossRef](#)]
79. Hafez, H.A.; Abdallah, A.; Hammad, M.; Hamdy, N.; Yassin, D.; Salem, S.; Hassanain, O.; Elhalaby, L.; Elhaddad, A. Outcomes of allogeneic hematopoietic cell transplantation for childhood chronic myeloid leukemia: Single-center experience. *Pediatr. Transpl.* **2020**, *24*, e13664. [[CrossRef](#)]
80. Gómez-Almaguer, D.; Cantú-Rodríguez, O.G.; Gutiérrez-Aguirre, C.H.; Ruiz-Argüelles, G.J. The treatment of CML at an environment with limited resources. *Hematology* **2016**, *21*, 576–582. [[CrossRef](#)]
81. Ohanian, M.; Kantarjian, H.M.; Quintas-Cardama, A.; Jabbour, E.; Abruzzo, L.; Verstovsek, S.; Borthakur, G.; Ravandiet, F.; Garcia-Manero, G.; Champlin, R.; et al. Tyrosine kinase inhibitors as initial therapy for patients with chronic myeloid leukemia in accelerated phase. *Clin. Lymphoma Myeloma Leuk.* **2014**, *14*, 155–162.e1. [[CrossRef](#)]
82. Geelen, I.G.P.; Thielen, N.; Janssen, J.J.W.M.; Hoogendoorn, M.; Roosma, T.J.A.; Willemsen, S.P. Treatment outcome in a population-based, ‘real-world’ cohort of patients with chronic myeloid leukemia. *Haematologica* **2017**, *102*, 1842. [[CrossRef](#)]
83. Jain, P.; Kantarjian, H.M.; Ghorab, A.; Sasaki, K.; Jabbour, E.J.; Noguera Gonzalez, G. Prognostic factors and survival outcomes in patients with chronic myeloid leukemia in blast phase in the tyrosine kinase inhibitor era: Cohort study of 477 patients. *Cancer* **2017**, *1235*, 4391–4402. [[CrossRef](#)] [[PubMed](#)]