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Management of Chronic Myeloid Leukemia (CML) in Children and Adolescents: Recommendations from the Children's Oncology Group CML Working Group

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Abstract

Chronic myeloid leukemia (CML) accounts for 2–3% of leukemias in children under 15 and 9% in adolescents age 15–19. The diagnosis and management of CML in children, adolescents and young adults have several differences compared to that in adults. This review outlines the

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diagnosis and management of the underlying disease as well as challenges that can occur when dealing with CML in this patient population.

Keywords

CML; Pediatric; Recommendations

Introduction

Chronic myeloid leukemia (CML) is a rare disease in children and adolescents accounting for 2% to 3% of all leukemias in children younger than 15 years of age and ~9% in adolescents between 15 to 19 years of age^{1,2}. The average annual incidence of CML in children younger than 15 years is 0.6–1.0 cases per million and that for patients 15–19 years of age is 2.1 per million³. Given the rarity of this diagnosis and very scant clinical trial data, current management recommendations are derived from studies or practice guidelines developed for adult patients with CML^{1–7}. However, children, adolescents and young adults tend to have a more aggressive clinical presentation than adults^{1,2,4,5}. Recent data indicate that some genetic differences exist in pediatric CML compared to adult disease^{8,9}; for example, 60% of pediatric patients have ASXL1 mutation compared to only 15% of adults¹⁰. Further, children with CML are exposed to their disease and its therapy during periods of growth and development, and a life-long treatment is required in most cases, for a much longer period of time compared to those who are diagnosed at a much later age; assuming that most patients require life-long therapy.

Tyrosine kinase inhibitors (TKI) are now standard of care for patients with CML in chronic phase^{6,7,11}. In addition to targeting the fusion protein of BCR-ABL1, the TKI may have off-target inhibition of other tyrosine kinases such as platelet derived growth factor receptor (PDGFR), vascular endothelial growth factors receptors (VEGFR), c-KIT etc., which share pathways for bone growth and metabolism and other endocrine functions^{12,13}. The long-term effects of TKIs on developing children are presently unknown and likely to be different than what is observed in adults. While newer and safer therapies are sought for CML in children, defining the safety and efficacy of existing TKI in children is important. However, currently there are no evidence-based guidelines for diagnosis and management of CML in children and adolescents.

The Children's Oncology Group (COG) CML Working Group identified these gaps in the management of CML in children. In the absence of pediatric specific evidence-based guidelines, it will be important to have uniform approach for management of CML in children. These recommendations will allow consistency in evaluation, management and follow-up of these patients and will enable collection of information for future studies in children and adolescents with CML.

Methods

To develop these recommendations, a list of frequently encountered questions in the management of different phases of CML in children and adolescents was developed

(Supplemental File, Appendix 1). This was followed by a descriptive literature review of original studies and expert opinion manuscripts evaluating management and outcome of CML in children and adolescents. In addition, published guidelines, guidance documents and standard of care documents for the management of adults with CML were reviewed^{1,2,4-11,14-21}. The data gathered were presented and reviewed within the COG CML Working Group. Based on the review, recommendations were developed.

Diagnosis of CML in Children and Adolescents

What information is required at the time of diagnosis of CML in children and adolescents?

The National Comprehensive Cancer Network (NCCN) guidelines recommend the following tests at diagnosis of CML: history and physical examination, spleen size (cm below costal margin), complete blood count (CBC) with differential, chemistry profile, bone marrow (BM) aspirate and biopsy and quantitative RT-PCR (Q-RT-PCR) using international scale from peripheral blood¹¹. In the aspirate the required tests include morphology with percentage of blasts and basophils, karyotype, fluorescent in situ hybridization (FISH) and qualitative RT-PCR for BCR-ABL1¹¹. Cerebrospinal fluid (CSF) studies are not required in patients with chronic phase (CP) CML unless clinically indicated or in patients with suspected blast phase (BP). These recommendations are also supported by the International Berlin Frankfurt Munster (I-BFM) Study Group Chronic Myeloid Leukemia Committee⁶.

Recommendation—The following investigations at diagnosis in all patients with suspected or confirmed CML: history and physical examination, spleen size (by palpation, report in cm below the costal margin), CBC with differential, BM aspirate and biopsy, BM karyotyping, FISH (BCR-ABL1), peripheral blood and/or BM Q-RT-PCR for BCR-ABL (Table 1). There is no need for CSF sampling in CML CP.

What further baseline investigations are needed at CML diagnosis?

NCCN guidelines recommend additional baseline tests including: extended chemistry, liver functions and human leukocyte antigen (HLA) typing¹¹. The Alberta guidelines also recommend baseline endocrine evaluations including lipase, glucose, cholesterol, hemoglobin A_{1c}, lipid profile and thyroid function¹⁹. Bone mineral density (BMD) at diagnosis might be helpful but there are currently no data in pediatric age group. HLA typing at diagnosis may be of use. Rhabdomyolysis is rarely reported with the use of TKI²². One may consider checking creatinine kinase in patients with spontaneous myalgia.

Recommendation—Recording exact height, weight, body mass index (BMI), Tanner stage, blood group, bone age, coagulation profile, renal functions, calcium, phosphate, liver functions, lipid profile, glucose, HbA_{1c}, baseline thyroid functions (thyroid stimulating hormone [TSH], free T4) and baseline serology per institutional guidelines (Table 1), in addition to prior vaccination record based on institutional guidelines. We feel that HLA typing at diagnosis may be of use.

How is advanced stage (blast phase or accelerated phase) CML defined at diagnosis or during therapy?

There is no universally accepted definition or consensus on accelerated phase (AP) or blast phases (BP) CML^{11,20}. The WHO classification defines BP as ≥20% blast cells in the peripheral blood or BM, or extramedullary blast proliferation, which can occur anywhere but most commonly seen involving the skin, lymph node, spleen, bone or central nervous system²¹. In adults, most BP are myeloid lineage with 20–30% being lymphoblastic²³. However, in pediatrics BP are predominantly lymphoblastic; an international registry of CML in children and adolescents (n=479) reported 17 children presenting with BP and 12/17 (70%) had lymphoblastic BP²⁴. Sheets of blasts may be seen in focal areas of the bone marrow, which can be considered evidence of a BP even if the rest of the marrow shows chronic phase²¹. Additionally, the presence of lymphoblasts even at lower number may herald blast transformation and requires further evaluation.

The European LeukemiaNet (ELN) uses different criteria to define AP and BP compared to WHO criteria (Table 2)^{20,21}. We recommend following WHO criteria as described below.

Accelerated phase (AP) is defined as presence of any one or more of following criteria by WHO²¹:

Persistent or increasing splenomegaly, persistent or increasing WBC count ($>10 \times 10^9/L$) unresponsive to therapy, peripheral blood basophils ≥20%, platelet count $>1000 \times 10^9/L$ uncontrolled by therapy or $<100 \times 10^9/L$ unrelated to therapy, 10–19% peripheral blood and/or BM blasts; any new clonal abnormality or additional clonal abnormalities in Ph+ cells at diagnosis (e.g. second Ph clone, trisomy 8 or 19, isochromosome 17q), and/or abnormalities of 3q26.2 or complex karyotype.

The following are provisional criteria for the diagnosis of CML AP²¹:

Poor therapy response (lack of hematological response to the first TKI or molecular indication of resistance to 2 sequential TKI) or occurrence of two or more mutations in BCR-ABL1 during TKI therapy.

Recommendation—Following WHO classification for definition of blast phase, accelerated phase and chronic phase for children and adolescents with CML^{20,21} (Table 2).

What is the utility of existing prognostic scoring systems in the context of CML in children and adolescents?

Scoring systems are commonly used to prognosticate and manage CML in adults, but most of them (SOKAL, Hasford and EUTOS) are not applicable to pediatrics^{14,25}. The newly devised EUTOS Long-Term Survival (ELTS) score based on age, spleen size, platelet count and peripheral blasts was shown to better discriminate the probability of death due to CML in adults¹⁴. The International Registry for Chronic Myeloid Leukemia (I-CML-Peds study) in children and adolescents evaluated and compared the risk group allocations and outcome between the prognostic scores in the pediatric population (n=350). This study showed that the ELTS score was associated with better differentiation of progression-free survival

compared to SOKAL, Hasford and EUTOS scores in children and adolescents with CML¹⁴. However, more pediatric data are required to confirm that ELTS is applicable to children and adolescents with CML.

Recommendation—Not to use the SOKAL, Hasford and EUTOS scores for risk assessment or treatment decisions for children with CML.

Management of CML in Children and Adolescents

When is leukapheresis indicated?

Leukapheresis in CML is not indicated simply based on a specific white cell count. In fact, most patients with a high WBC count do NOT need leukapheresis. Unlike in acute leukemias, the thrombosis and leukostasis risk associated with hyperleukocytosis is hypothesized to be less frequent in CML due to the preponderance of maturing WBCs rather than enlarged blasts that account for the leukocytosis in acute leukemia^{26,27}. Early initiation of hydroxyurea may help to decrease the WBC and reduce leukostasis risk without the need for apheresis.

Leukapheresis may be considered emergently if there are signs of leukostasis and end organ injury such as respiratory distress, priapism, severe retinopathy/papilledema or central nervous system (CNS) symptoms concerning for ischemic or hemorrhagic stroke²⁷. Leukapheresis is also useful and may be considered in the management of CML in pregnancy^{28,29}. If leukapheresis is used, additional medical treatment such as hydration, hydroxyurea (50–100 mg/kg/day given orally in 3–4 divided doses with a maximum dose of 6 gm) and TKI therapy should be initiated as soon as possible.

Recommendation—The decision of leukapheresis should be based on symptoms of leukostasis (such as respiratory distress, priapism, stroke) rather than the presenting WBC count alone. Leukapheresis can be of benefit in pregnancy.

What TKI should be used as initial therapy for CP CML in children and adolescents?

For adult patients, imatinib, dasatinib, nilotinib and bosutinib are all FDA approved as frontline therapy and recommended for frontline treatment according to NCCN guideline¹¹. Until recently imatinib was the only FDA approved TKI for first line therapy in children with CML^{6,15–17}. Dasatinib was approved by FDA as first and second line therapy for pediatric patients with CP CML in 2017¹⁸. Nilotinib has also been approved by FDA in 2018 as first and second line therapy for pediatric patients with CML one year or older^{30,31}. Bosutinib has recently been evaluated in the pediatric population³².

Although some European groups recommend a lower starting dose of imatinib in children with CP CML (260–300 mg/m²/day), based on the results of COG Phase II study using higher dose of Imatinib which was well tolerated, our preference for the initial recommended dose of Imatinib is 340 mg/m²/day (maximum dose 600 mg)^{2,33–36}. The starting dose of dasatinib in children with CP CML is 60 mg/m² once daily (maximum dose 100 mg). The dose of nilotinib identified for children with CP CML is 230 mg/m²/dose twice daily, with a maximum single dose of 400 mg^{30,31}. Second generation TKIs are likely

to induce faster and deeper molecular response but do not impact disease free survival^{37,38}. Appendix II (Supplemental file) describes pediatric dosage and dosing details for imatinib, dasatinib and nilotinib.

Recommendation—Based on availability imatinib (340 mg/m²/day, maximum dose 600 mg), dasatinib (60 mg/m² once daily, maximum dose 100 mg) or nilotinib (460 mg/m²/day in two divided doses) can be used as frontline TKI. TKI dose should be adjusted for body surface area but the maximum dose should not be exceeded.

How to monitor therapy response and disease status?

The response to TKI therapy is determined by measuring hematologic, cytogenetic and molecular responses (called the “milestones of response”). Hematologic response is defined as normalization of peripheral blood counts and regression of hepatosplenomegaly; cytogenetic response is defined as a decrease in the Ph-positive chromosomes in BM metaphases (a minimum of 20 metaphases should be analyzed) and a molecular response as a decrease in the amount of BCR-ABL1 chimeric mRNA using Q-RT-PCR and is expressed as a ratio of BCR-ABL1 mRNA transcripts to the mRNA transcripts, usually wild type ABL1 mRNA is used¹¹.

The I-BFM CML committee recommends Q-RT-PCR for BCR-ABL1 on the peripheral blood every 3 months⁶. They also recommend BM every 3 months until complete cytogenetic response (CCyR) is achieved followed by peripheral blood surveillance as long as there is no loss of response. The NCCN recommends peripheral blood Q-RT-PCR every 3 months for 3 years and then every 3–6 months¹¹. If there is a 1-log increase but major molecular remission (MMR) is still maintained, then peripheral blood Q-RT-PCR should be repeated in 1–3 months. They recommend BM evaluations at 3 and 6 months after diagnosis if Q-RT-PCR is not available, at 1-year after diagnosis if CCyR and MMR are not achieved and at 18-months if MMR is not achieved or if 1-log increase in BCR-ABL1 is seen without a MMR or loss of MMR.

Recommendation—Disease monitoring as outlined in Table 3¹¹.

How to define response to therapy?

In adult CML, response to TKI is the most important prognostic factor irrespective of the type of TKI used^{11,20}. ELN defines response as “optimal” or “failure”. The “optimal” response is associated with the best long-term outcome and indicates that no change in therapy is required, whereas “failure” indicates a change in therapy (either change of TKI or proceeding to stem cell transplant (SCT)). Between “optimal” or “failure” is an intermediate “warning” zone, meaning disease response needs more frequent monitoring to permit timely change in therapy²⁰. The NCCN has color coded the response milestones based on BCR-ABL1 transcript level as determined by Q-RT-PCR into red (indicative of failure and change of therapy), yellow (warning zone where close monitoring is required with or without change in therapy like increasing the dose of first line TKI or switching of TKI) and green indicating continue same TKI and monitoring response¹¹. Currently there are no comparable data to correlate cytogenetic or molecular response to outcome in pediatric patients with

CML. Hence, we recommend following response definitions and criteria based on adult recommendations from ELN and NCCN and some pediatric expert opinions^{6,7,11,20}.

Recommendation—Following response criteria based on modification from NCCN and ELN as outlined in Tables 4 and 5.

How to monitor compliance to TKI therapy?

Non-compliance is one of the most common reasons for suboptimal response and treatment failure in patients with CML on TKI³⁹. Non-compliance is a major problem in teen-agers and compliance often deteriorates during first year after a good response has been obtained⁴⁰. Patients should be educated regarding the importance of compliance to their TKI therapy. Patients should be asked about their compliance to therapy at every clinic visit with education and help provided to improve TKI compliance. There is no evidence to support routine monitoring of TKI levels to confirm compliance. However, when there is a concern of compliance a plasma trough level of TKI can be done: imatinib therapeutic drug monitoring (TDM) is now commercially available in North America. Adult studies have shown best response at trough target level > 1000 ng/ml^{6,40–43} and increased hematological toxicity at levels >3,180 ng/ml, but there are no pediatric data. TDM for other TKIs is not yet readily available. There are no data from the pediatric CML population.

Recommendation—Frequently educating patients regarding the importance of compliance to TKI therapy, and to discuss their compliance at every visit, providing additional help, as needed. Monitoring plasma level of imatinib can be considered if available and if there is concern about compliance.

When to do BCR-ABL1 kinase domain mutation analyses?

Primary resistance to TKI in patients with uncomplicated CML-CP is rare. Hence routine testing for mutations is not required at diagnosis of CML-CP or for those with an optimal response to TKI. Recommendations for mutational analysis are evolving. The NCCN recommends that mutation testing should be done in CP if there is an inadequate initial response; if there is evidence of loss of response; if there is a 1-log increase in BCR-ABL1 transcript or loss of MMR; or if there is disease progression to AP or BP¹¹. ELN guidelines recommend mutational analysis for patients with failure or progression to AP or BP²⁰. The GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) study found that genetic mutations were more frequent in patients with cytogenetic suboptimal response than those with molecular suboptimal response⁴⁴. The I-BFM CML committee recommends that mutational analysis should be done only if treatment failure or suboptimal response is observed⁶.

Recommendation—Mutational analyses be performed if a failure to achieve therapy milestones (suboptimal response) is observed, loss of prior response or progression to AP or BP.

What are the indications for adjusting or changing initial TKI?

The common indications for switching the initial TKI are if there is intolerance, intolerable toxicities, a mutation that causes resistance to specific TKI, or failure to achieve treatment milestones¹¹. If mutational analysis indicates a mutation specific to a TKI, further TKI selection should be made accordingly. TKIs ponatinib and bosutinib as well as omacetaxine have been developed for patients with TKI resistance²⁰.

Recommendation—Switching to a different TKI for intolerance, toxicity or resistance to or failure of a TKI.

Is there a role for stopping TKI in pediatric patients with a good response?

Several studies regarding stopping TKIs have been published in adults with deep and sustained molecular remission for over 2 years^{11,45,46}. Until recently, stopping TKI therapy in adult patients was recommended only in the context of a clinical trial. However, NCCN guidelines now recommend stopping TKI only for a select population who fulfill all of the following criteria^{11,20}: age ≥ 18 years with CP-CML on an approved TKI therapy for at least 3-years; prior evidence of quantifiable BCR-ABL1 transcript; stable molecular response (MR4; 0.01% IS) maintained for at least 2 years or longer; no history of TKI resistance; and access to reliable Q-RT-PCR testing with sensitivity of detection = 4.5 logs IS. Close monitoring, every 3 to 4 weeks, after stopping TKI is mandatory.

So far there are no data to show the feasibility of stopping TKI in the pediatric CML population. The limited available data are mainly based on case reports of non-compliant pediatric patients⁴⁷. Current adult guidelines for stopping TKI cannot be applied for children and adolescents without proper prospective clinical trials.

Recommendation—TKI therapy should only be stopped in children and adolescents in the context of a clinical trial.

What are the indications for allogeneic stem cell transplant (SCT) in children and adolescents with CML?

Thus far, SCT is the only known curative therapy for CML. However, given the risks of SCT, and overall few associated toxicities with TKI, medical therapy with TKI has essentially replaced SCT in both children and adults with CP CML. On the other hand, the need for life long therapy with TKI and the known and unknown late effects of TKI may make SCT an attractive option for some. Therefore, there remains controversy regarding the role of SCT in pediatric patients with CML-CP responsive to their first TKI therapy^{1,6,7,17,36}.

Currently, SCT is indicated when patients either present with or progress to BP or develop AP^{1,11,20}. A recent study from the International CML registry reported survival in some patients with BP (n=5) and AP (n=14) who were treated with TKI without SCT with or without systemic chemotherapy²⁴. Further studies are required to evaluate the role of TKI and systemic therapy alone without SCT for long term survival of patients presenting with advanced stage disease at diagnosis. However, the above study indicates that it is possible to

treat some patients who present with AP without SCT, especially if there is no suitable donor; all efforts must be undertaken to search for a suitable donor. Additionally, failure of or intolerance to TKI may be also considered indications for SCT^{11,20}.

There is no clear answer regarding the role of SCT in non-compliant patients. The I-BFM CML Committee recommends SCT in the setting of poor TKI compliance despite maximum support; or serious side effects from TKI; or following appropriate patients/family counselling regarding the risk of SCT versus the probability of achieving definitive cure with SCT over TKI therapy alone⁶. To date there have been no randomized trials comparing TKI and SCT. Although SCT can be curative, there remains the risk of substantial transplant related morbidity and mortality, including infertility and long-term complications, and the risk of later relapse¹⁵. With recent advances surrounding SCT, children undergoing transplant have fewer complications and better outcomes compared to adults and hence SCT may be an option for patients who cannot or do not want to continue lifelong TKI therapy^{1,36}.

Accepted criteria for SCT are:

- i. Blast phase or accelerated phase at diagnosis;
- ii. Progression to BP or AP once in chronic phase;
- iii. Failure of multiple TKIs (has not met response criteria or progressing);
- iv. Presence of unacceptable or intolerable toxicity to TKI;
- v. Role of SCT is arguable in patients with poor compliance. Of note, compliance is also necessary for SCT medications (e.g. GVHD prophylaxis).
- vi. Patient preference. There should be a detailed discussion on pros and cons especially with patients in first CP.

Recommendation—SCT for pediatric patients who either present with or progress to BP or AP; SCT may also be considered for patients who have failed two TKIs or have intolerable toxicities to TKI. SCT could be offered to adolescents and children with serious compliance issue in CML-CP only after a detailed discussion of risks and benefit of SCT.

Toxicities of Therapy for CML

TKIs have toxicities that require monitoring in children receiving them. These toxicities can occur in many organ systems, but are most often endocrinological, as well as hematological and systemic.

Endocrine Toxicities

Bone Density

TKIs are known to have an effect on bone metabolism, however recommendations for monitoring bone health have varied. Aleman and colleagues have described how TKIs cause secondary hyperparathyroidism, hypophosphatemia with phosphaturia¹³. There may be other contributing causes of hypophosphatemia as well. Osteoclast activity, which is

important for bone remodeling, is reduced¹³. Aleman et al recommended that patients on imatinib ingest adequate calcium and vitamin D to help reduce secondary hypoparathyroidism. TKIs also alter calcium and phosphate metabolism so clinicians should check calcium, phosphorous, parathyroid hormone (PTH) and vitamin D levels 6 weeks after the start of TKI and follow up every 6 months thereafter¹⁵. If there is a fracture or decreased bone mineral density on plain radiograph, then patients should undergo bone densitometry (DEXA scan). The I-BFM CML Committee recommends a DEXA scan every 5 years in children receiving imatinib⁶. The NCCN recommends DEXA scan if the BMD is decreased on a plain radiograph or if there is an unprovoked fracture¹¹.

Recommendation—DEXA scan be obtained at baseline and yearly after for children and adolescents on a TKI. Laboratory monitoring should include calcium, phosphorous, PTH and 25-hydroxy vitamin D at baseline and every 6 months thereafter. Patients should be encouraged to have an adequate dietary intake of calcium. Clinicians should seek to maintain 25-hydroxy vitamin D in the optimal range (30 ng/ml) and may need to recommend vitamin D supplementation with ergocalciferol or cholecalciferol to achieve that.

Growth

All TKIs can affect growth in patients who are pre-pubertal. Multiple authors have described impaired longitudinal growth in children on TKI, mostly seen in pre-pubertal children (for an overview see Samis et al¹²). The growth failure is felt to be due to inhibition of the activity at non-BCR-ABL1 enzymes, including inhibition of PDGFR-beta signaling and results in decreased recruitment and activity of chondrocytes in the growth plate, and dysregulated bone remodeling due to reduced osteoclast activity¹².

Recommendation—Growth parameters (height, weight and BMI) should be obtained at baseline and every 3 months thereafter. A bone age should be obtained if the linear growth (height velocity) is slow such that the patient is experiencing a decline in height percentiles.

Puberty Delay

The effects of TKIs on puberty are inconclusive so recommendations exist that at an adequate age, pubertal development should be monitored every 4–6 months¹². If there is delayed puberty or sex steroid deficiency then further workup is warranted including measuring gonadotropins, sex steroids and bone age.

Recommendation—Puberty assessment be obtained at baseline and starting at 8 years every 6 months until puberty completion. Gonadotropin and sex steroid testing should be obtained at baseline and later during treatment if puberty is delayed or if symptoms of sex steroid deficiency develop in the post-pubertal adolescent.

Fertility and Reproductive Health

There are reported effects of all the TKIs on reproductive health. Imatinib, dasatinib and nilotinib are all considered teratogenic and have caused embryonic or fetal toxicities in

animal studies¹⁵. Imatinib and its metabolites are also known to be excreted in human milk^{15,48}.

The NCCN guidelines state that TKI therapy does not seem to have an effect on male fertility or cause fetal malformations in a male partner's pregnancy¹¹. However, current TKI therapy at the time of conception and during pregnancy in women has been reported to be associated with fetal abnormalities and spontaneous abortions¹⁵.

Recommendation—For post-pubertal boys, sperm banking should be offered prior to undergoing stem cell transplant. For girls, reproductive endocrinology and/or fertility consult may be offered at diagnosis and pregnancy should be avoided while on TKI.

Other Endocrine Effects

There are other endocrine effects such as thyroid dysfunction, which is a well-known side effect of TKI¹². An increased risk of subclinical glucocorticoid deficiency has been reported in patients receiving imatinib. TKIs can affect glucose metabolism causing hypoglycemia or hyperglycemia, and nilotinib has been associated with hyperglycemia¹². Special attention to fluctuations in glucose are particularly important in patients with pre-existing diabetes mellitus prior to CML diagnosis.

Recommendation—Baseline thyroid function testing (TSH and free T4), glucocorticoid metabolites (morning serum cortisol) and HbA_{1c}. These tests should be followed annually or sooner if symptoms of hypothyroidism, adrenal insufficiency, or glucose abnormalities occur.

Other Side Effects

Other Common Acute Side Effects

All TKIs have several side effects in common (so-called class effects) including neutropenia and thrombocytopenia, anemia, infection, rash, nausea, edema, muscle cramps, bone pain, diarrhea, lethargy, and weight gain⁶. A detailed list of side effects associated with the various TKIs, reported in pediatric and adult studies, is found in Table 6^{6,15,17,48,49}, and monitoring recommendations during ongoing TKI therapy are found in Table 1.

Other Considerations in Pediatric CML Therapy

Immune Suppression

There are little data on immune function in patients on TKI therapy. There is some immune suppression with TKI therapy, however, immune suppression by TKIs does not seem to be at a degree to cause concern for opportunistic infections⁵⁰. Pneumocystis jiroveci pneumonia (PJP) prophylaxis is not needed with TKI therapy.

Immunizations can be given while on TKI therapy with some exceptions. In general, administration of inactivated killed vaccines to children on TKI therapy is safe, though the response may be insufficient^{15,17}. Live attenuated vaccines are not recommended although one study showed that varicella vaccine could be given safely to children with immune

deficiency thus could be considered in children on TKI therapy⁵¹. The NCCN guidelines recommend that live vaccines may be considered after stopping TKI for several weeks in patients with deep molecular response, if needed¹⁵.

Recommendation—Killed vaccines are safe and live vaccines may be considered after stopping TKI several weeks if the patient is in deep molecular response.

Transition to Adult Care

Transitioning of pediatric patients with CML to adult care should be individualized. In general, transition to adult care often occurs at age 18–21 as most oncologists surveyed by the Children’s Oncology Group felt that they provided appropriate care up to age 21^{52,53}. It is important to have a smooth transition to the adult setting when this change in provider does occur to ensure a successful transition⁵². Some oncologists advocate transfer at age 18 because there may be clinical trials available for patients at an adult center which may be of benefit to the patient.

Recommendation—Patients should be transferred to adult care providers between the ages of 18–21, but if there is a clinical trial available at the adult center then transition may occur as soon as the patient is eligible for the trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations Used

CML	Chronic myeloid leukemia
TKI	Tyrosine kinase inhibitors
PDGRF	Platelet derived growth factor receptor
VEGFR	Vascular endothelial growth factor receptors
COG	Children’s Oncology Group
NCCN	National Comprehensive Cancer Network
CBC	Complete blood count
BM	Bone marrow
Q-RT-PCR	Quantitative RT-PCR

CSF	Cerebrospinal fluid
FISH	Fluorescent in situ hybridization
CP	Chronic phase
BP	Blast phase
AP	Accelerated phase
BMI	Body mass index
I-BFM	International Berlin Frankfurt Munster
ETLS	EUTOS Long-Term Survival
HLA	Human leukocyte antigen
BMD	Bone mineral density
TSH	Thyroid stimulating hormone
ELN	European LeukemiaNet
CMV	Cytomegalovirus
CNS	Central nervous system
CCyR	Complete cytogenetic response
MMR	Major molecular remission
SCT	Stem cell transplant
TDM	Therapeutic drug monitoring
GIMEMA	Gruppo Italiano Malattie EMatologiche dell' Adulto
IS	International scale
MR	Molecular response
PTH	Parathyroid hormone
PJP	Pneumocystis jiroveci pneumonia

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Table 1.

Initial evaluation and follow up investigations

Evaluation		At diagnosis	Follow up
History & Physical		X	Every visit
Spleen size (by palpation) cms below costal margin		X	Every visit
Ht/Wt/BMI		X	Every visit
Tanner staging		X	Every 6 months
CBC with differential & Platelets		X	Every 3 months
% blasts		X	
Peripheral blood QRT- PCR		X	Every 3 months *
Bone marrow Aspiration		X	At 3 months and 1 year
	Morphology	X	
	% blasts	X	
	% basophils	X	
	Karyotype	X	One year
	FISH	X	
	Quantitative RT-PCR	X	
Bone Marrow Biopsy		X	
Other tests		X	
Blood group		X	
Coagulation profile	INR/APTT	X	
Cardiac evaluation	ECHO	X	Annually
	EKG with QT interval	X	Annually
Chemistry	Extended chemistry with renal and liver functions	X	Every 3 month
	Lipase	X	Every 3 month
	Glucose	X	Every 3 month
	Urate	X	Every 3 month
	Cholesterol	X	Every 3 month
	HbA1C	X	Every 3 month
	Lipid profile	X	Every 3 month
	Thyroid functions	X	4-6 weeks after TKI therapy and then annually
	HLA testing	X*	-
Virology	CMV, hepatitis pane, varicella zoster	X	

* HLA typing may be of use at diagnosis. But it can be done later.

Abbreviations

cms= centimetres; ht= height; wt= weight; BMI=body mass index; CBC= complete blood count; QRT-PCR= quantitative reverse transcriptase polymerase chain reaction; FISH= fluorescent *in situ* hybridization; INR= international normalizing ratio; APTT= activated partial thromboplastin

time; ECHO= echocardiogram; EKG= electrocardiogram; HLA= human leukocyte antigen; CMV= cytomegalovirus; TKI= tyrosine kinase inhibitor

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Table 2.

Clinical and hematological criteria for the definition of chronic phase, accelerated phase and blast crisis according to WHO classification^{20,21}

CML-Chronic Phase	CML-Accelerated Phase*	CML-Blast Phase*
Presence of all of the following criteria	Presence of any or all of the following criteria	Presence of any or all of the following criteria
Less than 10% blasts in the peripheral blood and BM	Peripheral blood or BM blasts 10–19% (ELN criteria: blasts in blood or BM 15–29% OR blasts plus promyelocytes in blood or BM >30% with blasts <30%)	Peripheral blood or BM blasts WBC or nucleated BM cells (ELN Criteria: blasts in blood or BM 30%)
Does not meet any criteria for accelerated phase or blast crisis	Persistent or increasing WBC count unresponsive to therapy	Extramedullary blast proliferation (Same as ELN)
	Persistent thrombocytosis $>1000 \times 10^9/L$ uncontrolled by therapy or persistent thrombocytopenia $<100 \times 10^9/L$ unrelated to therapy (ELN criteria uses only thrombocytopenia as described by WHO)	Larger foci or clusters of blasts on BM biopsy
	Peripheral blood basophils 20% (Same as ELN)	
	Persistent or increasing splenomegaly	
	Any new clonal abnormality or additional clonal abnormalities in Ph+ cells at diagnosis (second Ph clone, trisomy 8 or 19, isochromosome 17q), abnormalities of 3q26.2 or complex karyotype. (Same as ELN)	Red flag: bona-fide lymphoblasts in the blood or BM, even if <10%, may indicate imminent lymphoblastic transformation and warrants further clinical and genetic investigations
	Provisional criteria	
	<ul style="list-style-type: none"> Poor therapy response (lack of hematological response to first TKI or molecular indication of resistance to 2 sequential TKI) or occurrence of mutations in BCR-ABL1 during TKI therapy 	

* Information in parenthesis compares and contrasts to ELN Criteria

Abbreviations:

CML= chronic myeloid leukemia; BM= bone marrow; WBC=white blood cells; TKI= tyrosine kinase inhibitor; ELN= European LeukemiaNet; WHO= World Health Organization

Table 3.Disease monitoring based on NCCN Recommendations¹¹

	Recommendations
History and physical examination with documentation of spleen size by palpation (indicate cm below costal margin)	Every visit- Weekly until clinically stable Biweekly till complete hematological response Then monthly till 3 months from diagnosis and then every 3 months
CBC with differential	Every visit
BM Karyotyping	Every 3 months until complete cytogenetic response Failure to achieve response milestone Any sign of loss of response (defined as hematologic or cytogenetic relapse)
PB Q-RT-PCR	At diagnosis Every 3 month until CCyR and then every 3 month for 2 years and then every 3 to 6 months. With 1 log increase in with MMR repeat in 1–3 months.
BCR-ABL kinase domain mutation analysis	<ul style="list-style-type: none"> • In chronic phase if • inadequate initial response • Any sign of loss of response or • 1-log increase in transcript or loss of MMR • Disease progression to AP or BP

Abbreviations

NCCN= National Comprehensive Care Network; CBC= complete blood count; BM= bone marrow; PB= peripheral blood; Q-RT-PCR= quantitative reverse transcriptase polymerase chain reaction; CCyR= complete cytogenetic response; MMR= major molecular remission; AP= accelerate phase; BP= blast phase

Table 4. Criteria to define response to TKI therapy in children and adolescents with CML-CP

Type of response	Anticipated duration to response
Complete hematologic response	No signs and symptoms of disease with disappearance of palpable spleen Complete normalization of peripheral blood count with WBC count within age appropriate normal values Absence of immature cells such as myelocytes, promyelocytes or blasts in peripheral blood Platelet count within the normal range 150 – 450X 10 ⁹ /L
Cytogenetic response (a minimum of 20 metaphases should be analyzed)	Complete (CCyR)
	Partial (PCyR)
	Major (Complete + partial)
	Minor
Molecular response	>35%–65% Ph positive metaphases
	No detectable BCR-ABL1 mRNA by Q-RT-PCR (IS) using an assay with a sensitivity of at least 4.5 logs below the standardized baseline
	BCR-ABL1 transcripts 0.1% by Q-RT-PCR (IS) or more than a 3-log reduction in BCR-ABL1 mRNA from the standardized baseline, if Q-PCR according to IS is not available
Relapse	Any sign of loss of response (defined as hematologic or cytogenetic relapse) 1 log increase in BCR-ABL1 transcript levels with loss of MMR should prompt marrow evaluation for loss of CCyR and mutational analysis but is not defined as relapse

Abbreviations

CML= chronic myeloid leukemia; CP= chronic phase; TKI= tyrosine kinase inhibitor; Ph= Philadelphia; Q-RT-PCR= quantitative reverse transcriptase polymerase chain reaction; CCyR= complete cytogenetic response; MMR= major molecular remission; IS= international scale; AP= accelerate phase; BP= blast phase

Table 5.

*Acceptable time line for therapy response for first line TKI^{6,7,11,20}

Time in months	Optimal Response	Warning signs		Failure to respond	Clinical considerations for patients with warning signs or failure to respond
		Hematological and cytogenetic	BCR-ABL1 (IS)		
Diagnosis	NA	Blast crisis or AP; del(9q-); additional cytogenetic abnormalities in Ph+ cells	Baseline level	NA	Evaluate for SCT
3	CHR, BCR-ABL1 10% and/or Ph+ 35%	Ph+ 36-95%	>10%	No CHR; stable disease or disease progression Ph+ >95%	
6	BCR-ABL1 <1% CCyR, (Ph+ 0%)	Ph+ 1-35%	1%-10%	Ph+ > 35% BCR-ABL1 >10%	Evaluate patient compliance Evaluate drug interactions Mutational analysis Switch to alternate TKI and evaluate for SCT
12	CCyR BCR-ABL1 0.1%	-	>0.1% -1%	Ph+ 1% BCR-ABL1 > 1%	
18	BCR-ABL1 0.1%	-	>0.1% -1%		
Then and at anytime	-	Additional cytogenetic abnormality in Ph- cells	Any rise in BCR-ABL1 transcript level	Loss of CHR; loss of CCyR; presence of new mutation; loss of MMR; additional cytogenetic abnormality in Ph+ cells	

* Modified from references 6, 7, 11 and 20.

Abbreviations

IS= International scale; NA= not applicable; AP= accelerated phase Ph= Philadelphia; CHR= complete hematological response; PCyR= partial cytogenetic response; CCyR= complete cytogenetic response; MMR= major molecular remission; SCT= stem cell transplant; TKI= tyrosine kinase inhibitor

Table 6.Common Acute/Subacute Side Effects Seen with TKIs^{6,15,17,48,49}

	Imatinib	Dasatinib	Nilotinib	Ponatinib	Bosutinib
Side Effect	(% grade 3-4)	(% grade 3-4)	(% grade 3-4)	(% grade 3-4)	(% grade 3-4)
Neutropenia	1-10	1-10	1-10	1-10	1-10
Thrombocytopenia	1-10	1-10	1-10	1-10	1-10
Anemia	1-10	1-10	1-10	1-10*	1-10
Skin Rash	2-3	0-2	1-2	4-5	2-8
Nausea/Vomiting	1-2	2	<1	<1	1-5
Edema	1-6	<1	<1	<1	<1
Muscle Cramps	2-5	1-3	1-2	1-2	<1
Bone Pain	2-5	1-3	1-2	1-2	<1
Diarrhea	1-4	<1	1-2	1-10	1-12
Lethargy	1-2	1-4	1	1-2	1
Weight Gain	1-6	<1	<1	<1	<1
Abnormal LFTs	1-3	<1	<1	<1	<1
Hyperlipidemia	low	low	low	low	low
Short Stature	low	low	low	low	low
Thyroid Dysfunction	low	low	low	low	low
Pleural Effusion		2-11	<1		2-4
Pericardial Effusion		1-5			<1
Pulmonary Arterial Hypertension		1-2			
Avascular Necrosis	reports				
Elevated Pancreatic Enzymes	<1		1	3-20	
Increase Bilirubin			1		
Constipation			1		
Folliculitis Like Skin Rash			reports		
Increased Fasting Glucose	<1		1-5		
Decreased Blood Glucose	reports	reports			
Peripheral Arterial Occlusive Disease			1-5	1-5	5
Cerebral Ischemia			reports		
Myocardial Infarction			reports		
Vascular Adverse Events			reports		reports
QT Prolongation			<1	2	<1
Arterial Hypertension				reports	reports
Arterial and Venous Thromboembolic Events				1-5	
Exanthema					reports
Headache	<1	<1	1-2	1-3	1

Legend - Low - indicates level of grade 3-4 not available; Reports - indicates case reports for this side effect

Abbreviations: TKI= tyrosine kinase inhibitor; LFT= liver function test.