

Chronic myeloid leukemia in children: A brief-review

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ABSTRACT

Chronic myeloid leukemia (CML) in children is rare. The disease biology is the same as adults. Managing CML in children is challenging because of various issues like the rarity of the disease, lack of uniform guidelines, need of long-term medications, ensuring compliance and many more. This is a brief overview of some of these issues.

Key words: Children, chronic myeloid leukemia, hydroxyurea, tyrosine kinase inhibitors

INTRODUCTION

Chronic myeloid leukemia (CML) is the classic chronic myeloproliferative disorder defined as a clonal stem cell disorder resulting from the acquisition of an oncogenic breakpoint cluster region (BCR)/Abelson leukemia (ABL) fusion protein leading to the proliferation of granulocytic elements at all stages of differentiation. It is often called as the disease of “firsts” because of many interesting historical facts. The incidence of CML increases with age, with a peak incidence of 53 years.^[1] It is extremely rare in childhood.

CHRONIC MYELOID LEUKEMIA IN CHILDREN

Chronic myeloid leukemia constitutes around 3% of leukemia in the children and adolescent age group, with an annual incidence of 1 in 1000,000. About 110–120 pediatric and adolescent CML cases are seen each year in the United States.^[2] Children constitute around 10% of the total CML cases. Its rarity is established by the following facts. A phase one study from the children’s oncology group included

31 patients from 23 centers, signifying the rarity of CML in this age group.^[3] A comparison between imatinib (IMA) and stem cell transplant (SCT), as a therapy for childhood CML, included 30 patients in the IMA arm and 18 patients in the SCT arm.^[4] In other studies, the patient number varied from 4 to 39.^[5,6] In India, the age-specific incident rate of 0.04/100,000 was reported during 2001–2005.^[7] The median age at presentation was reported as 11–12 years.^[8] This varies in different studies depending on the differences in the age criteria. To derive further data on this rare disease and to formulate a treatment protocol, CML paed II trial is recruiting patients.^[9]

PATHOGENESIS

Chronic myeloid leukemia results from the reciprocal translocation of genes on chromosome 9 and 22. This leads to juxtaposition of the BCR gene on chromosome 22 with the virus ABL gene. The fused BCR-ABL protein has constitutive tyrosine kinase activity. It activates a number of intracellular signal transduction pathways like signal transducer and activator of transcription (STAT), renin-angiotensin system, JUN, MYC, and phosphatidylinositol-3 kinase. This plays an important role in increasing myeloid proliferation and suppressing apoptosis manifesting clinically as CML. For details, readers are advised to read an excellent article by Deininger *et al.*^[10] At the molecular level, the disease biology is same in adults and children.^[11] The three phases of CML are chronic phase (CP), accelerated phase (AP), and the blast phase (BP), the first being the most common way of presentation.

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PRESENTATION

The data on clinical presentation of CML in children is sparse. In an analysis, we noticed that the median age at presentation of CML in children and adolescent age group was 16 years. Male sex predilection was seen. The CP was the most common phase at presentation. The predominant symptoms at presentation were asthenia and splenic discomfort. The most predominant clinical sign was splenomegaly. The clinical presentation and the laboratory parameters like the median hemoglobin, median white blood cell (WBC), and the median platelet count in this age group did not differ in comparison to the adults.^[12] Frederic Millot *et al.* however reported the presenting leukocyte counts to be higher in children.^[13] The phase wise presentation is similar to adults with CML-CP being the predominant type. In the European analysis presented in the form of abstract out of the 51 patients 47 presented in CP. The details about the clinical features at presentation are eagerly awaited.^[14]

DIAGNOSIS

Chronic myeloid leukemia is suspected based on the classical symptoms, signs and laboratory parameters at presentation. Good examination of the peripheral smear suggests CML. The diagnosis is confirmed with conventional cytogenetic studies, by fluorescence *in situ* hybridization for *BCR-ABL* or by reverse transcriptase polymerase chain reaction. The different phases are diagnosed based on the WHO criteria.^[15]

TREATMENT

Historically, various treatment options were used like arsenic, splenic irradiation, splenectomy, busulfan, interferon (IFN) etc., and then came hydroxyurea (HU).

Interferon

Interferon was used in adults with or without cytarabine. It showed prolongation in the survival rates in adults. However, it is associated with many side effects like the myalgia, flu like symptoms, depression, autoimmune disorders of the thyroid leading to intolerance to this therapy. There are not many studies demonstrating the efficacy of IFN in childhood CML. In an analysis by Giona *et al.* a cytogenetic response (CyR) was achieved in 11 of 17 evaluable patients treated with IFN (65%): Complete CyR (cCyR) in four and partial in seven; the median time to achieve maximal CyR was 12 months and the projected 8 years survival of all patients treated with IFN was 63%.^[16] The results suggested the probable role of IFN in childhood CML. However due to the high intolerance rate and availability of better alternatives it is not a primary drug used in childhood CML.

Hydroxyurea

Hydroxyurea established its superiority to busulfan in adult CML patients in a German trial.^[17] In the current era, it is the most common drug used to control WBC count till the diagnosis is confirmed. It is also used as a palliative means in patients who cannot afford the definitive treatment. Treatment is begun with a dose of 25–50 mg/m²/day. The safety issues of this drug in children is often debated but based on the trials in sickle cell disease it appears to be a safe option. The role of HU in CML reduced after the introduction of the tyrosine kinase inhibitors (TKIs).

Tyrosine kinase inhibitors in chronic myeloid leukemia

Imatinib received accelerated approval from the US Food and Drug Administration in 2003 for use in pediatric CML and currently is considered the best front-line treatment for CML. Its efficacy was shown by many groups.^[18,19] The pharmacokinetics of IMA in children was studied by Petain *et al.* and it was found that IMA 260–340 mg/m²/day correspond to adult doses of 400–600 mg.^[20] The adverse event profile is same as the adults. The adverse event specific to this age group is longitudinal growth retardation which needs careful monitoring.^[21,22] In the CML-pead II trial, CML-CP patients were treated with IMA 300 mg/m² once daily, while in AP or in BP the dose was increased to 400 mg/m² and 500 mg/m² (bis daily), respectively. The drug was tolerated well as only 10% patients stopped it due to intolerance. In CML-CP patients, complete hematological response was documented in 95% at 3 months, 93% exhibited cCyR at month 12 and 85% patients achieved major molecular response (MMR) at 18 month after start of IMA. Thus, the trial showed high response rates with IMA similar to adults justifying its role as first line therapy for CML-CP in children. The children who could not tolerate IMA received dasatinib.^[14]

Dasatinib is well tolerated in children up to a dose level of 120 mg/m² and is effective, too.^[23] It is the first drug of choice in CML-AP and CML-CP [Table 1] because it provides more rapid response and greater 3 years event free survival (EFS) compared with standard-dose or high-dose IMA. Nilotinib is also an option available to treat CML in children. The choice between the two second generation TKIs is dictated by their adverse event profile.

Administration of TKIs to children is a challenge. The TKIs are available only in the tablet formulation which is not

Table 1: Preferred upfront treatment according to different phases of CML

CML phase	Upfront treatment
CML-CP	Imatinib
CML-AP	Dasatinib/nilotinib
CML-BP	Dasatinib/nilotinib

CML: Chronic myeloid leukemia, CP: Chronic phase, AP: Accelerated phase, BP: Blast phase

preferred by the children. Providing acceptable taste and accurate dose is often difficult thus affecting the compliance and response. This issue can be tackled by preparing liquid suspensions.^[24] Daily administration of TKIs prove to be a daily headache for many parents. The side effects to TKIs add to this problem.

The TKIs are not free of adverse events. Explaining them to children and their early recognition is often faced challenge. Children often find difficulty in adjusting with the common side effects of the drug like gastrointestinal toxicity. Moreover, rare possible disturbances of bone metabolism and longitudinal growth impairment are also of special concern in this age group.^[25] Further data from the CML-paed II trial will put some light on this adverse event.

UPFRONT TYROSINE KINASE INHIBITORS VERSUS ALLOGENIC-STEM CELL TRANSPLANT

Another commonly discussed issue pertaining to the management of CML in this age group is the debate of upfront TKIs versus allogenic SCT (allo-SCT).

Few arguments in favor of allo-stem cell transplant

1. Allogenic-SCT is the only known potentially curative therapy. The European Group for Blood and Marrow Transplantation data suggests overall survival at 3 years of 75% and 65% after sibling allo-SCT and unrelated donor SCT for childhood CML-CP. The transplant related mortality (TRM) was 20% and 30% in the respective groups.^[26] The 5 years EFS reported from the CML-pead I trial was 87% in matched related SCT, 52% in matched unrelated and 45% in the mismatched unrelated SCT.^[27] Thus, allo-SCT offers a possibility of curing childhood CML with a significant advantage for patients transplanted using matched related sibling donor
2. Data also suggest good outcomes if transplant is done early rather than done after disease progression. In the French trial, the EFS was better and the probability of relapse was lower in children who were transplanted in CP than those in AP.^[28]

Few arguments against allo-stem cell transplant

1. The outcomes of treatment for childhood CML has definitely improved with the introduction of TKIs. In order to evaluate the impact of IMA in childhood CML the Japanese investigators compared the outcomes of 12 CML children treated with IMA between 2001 and 2007 retrospectively with those of 16 children who underwent HSCT between 1984 and 2000. They noticed that the progression to advanced phase was lower and the EFS were better in the IMA arm. The survival curve

of the SCT group did not reach a plateau even 10 years after diagnosis.^[29] Thus, IMA has a definite impact on the survival of children with CML raising doubt about the need of upfront SCT

2. The long duration of therapy and the accompanying adverse events is an often used argument against the use of TKIs as upfront therapy for CML in children. Current studies have shown that TKIs are well tolerated by the children and the intolerance rate is same as that of adults. In contrast, the SCT therapy is also not free of the need of long-term medications. Many need medications for graft versus host disease (GVHD) for long duration after the SCT. In addition, the possibility of need of TKIs after SCT cannot be ruled out as many patients are treated with TKIs post SCT for the minimal residual disease or relapse both overt and incipient. Needless to mention that the duration of therapy for a subset of CML might not be long-term as the concept of cure with TKIs is evolving.^[30] STop IMatinib (STIM) and European stop kinase inhibitor (EURO SKI) are some of the trials looking into this matter [details available at www.clinicaltrials.gov]. Hopefully, the outcomes of these trials will help us determine the duration of TKI therapy
3. The SCT option is associated with risk of mortality (TRM) and morbidities. The French reported TRM of 90% with GVHD as the most frequent cause of death.^[28] This fact raises the question why to expose children to therapy which is potentially life threatening and associated with morbidity when good alternative therapy is available. In addition, not everyone has HLA matched sibling donor. The outcomes are poor with SCT from unrelated donor.^[28] All these arguments restrict the upfront use of allo-SCT for childhood CML.

ROLE OF STEM CELL TRANSPLANT

Allogenic SCT was the standard of care before the introduction of TKIs. Newer generation TKIs have probably reduced the need of this modality of therapy. The use of TKIs before transplant is associated with improved outcomes.^[31] Transplant physicians consider allo-SCT after suboptimal response/failure/resistance to TKIs and in advanced phases of CML. Strategies to manage residual disease after SCT include reduction of immunosuppression, donor lymphocyte infusion (DLI) and TKIs. Use of DLI has shown efficacy in relapse cases, of course, not without the risk of GVHD. Thus, the role of SCT as upfront therapy is getting restricted with the upfront use of TKIs.

MONITORING

Monitoring is needed to assess the treatment response (hematologic, cytogenetic and molecular), short- and

long-term side effects in particular, the development of IMA resistance, intolerance, noncompliance or progression to advanced-phase disease which must be identified in a timely fashion. Monitoring is performed at indicated time points or when suspicion of the disease recrudescence arises.^[32] There are no established and separate guidelines for monitoring the disease in this age group. Most of the people follow the European Leukemia Net guidelines as for the adults.^[29] The definitions for different response criteria are mentioned in Table 2.^[32] The best assessment of response is by the molecular tests as MMR is the best predictor of survival. The concept of achieving greater or deeper MRs is gaining popularity. Mutation analysis is indicated in case of TKI response failure. For toxicity grading and evaluations American National Cancer Institute Common Toxicity Criteria are followed. I suggest reading an elaborative article on this topic by Hari Menon.^[33]

ADVANCES

The recent major advances in the management of CML are:

Evolution of the concept of cure

The concept of “operational cure” proposed by Professor Goldman revolves around the idea that patients can enjoy the benefits of disease control after TKI without the need for ongoing treatment.^[34] This concept is gaining popularity and many studies like STIM trial, CML-8 trial, EURO SKI and STIM-2 are looking at this issue seriously.

Advances in the molecular monitoring

At the molecular level (MR) the disease can be traced to a much deeper level than it was possible earlier. In this regard, new parameters of monitoring like MR⁴, MR^{4.5}, MR⁵ are evolving.

Newer drug targets

Newer drugs to target the leukemic stem cells are being developed. These drugs act by targeting JAK/STAT, JAK2 kinase, a protein phosphatase 2A, arachidonate

5-lipoxygenase gene, histone deacetylases, sirtuin 1, and BCL6.

TAKE HOME MESSAGES

1. Most of the presenting features of CML in the children and adolescent age group are similar to those of the adults
2. Imatinib is effective and well tolerated in this age group
3. Therapy should be monitored properly especially for the long-term side effects
4. The two important challenges faced are treatment of advanced disease and compliance to treatment
5. The treatment of CML is still evolving.

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Table 2: Definition of response

Time points	Optimal	Suboptimal	Failure
3 months	CHR	<CHR	No HR
6 months	≥PCgR	<pCgR	No CgR
12 months	CCgR	<CCgR	<PCgR
18 months	≥MMR	<MMR	<CCgR
Any time	No loss of response	Loss of MMR Mutations ^a	Loss of CHR Loss of CCgR Mutations ^b

KD: Kinase domain, ABL: Abelson leukemia, BCR: Breakpoint cluster region, WBC: White blood cell, CHR: Complete haematological response (WBC <10×10⁹/l, differential with no immature granulocytes and <5% basophils, platelet <450×10⁹/l, spleen nonpalpable), PCgR: Partial cytogenetic response (Ph+metaphases 1%-35%), CCgR: Complete cytogenetic response (Ph+metaphases absent), MMR: Major molecular response (BCR-ABL: ABL<0.10% by international scale, on RT-Q-PCR). ^aBCR-ABL KD mutations still sensitive to imatinib, ^bBCR-ABL KD mutations still insensitive to imatinib

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