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## *Chronic myeloid leukemia: a review*

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# Chronic myeloid leukemia: a review

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**Abstract:**

**Background:** *Chronic myeloid leukemia remains a rare disease in children accounting for 2-3% of all childhood leukemias.The field has witnessed great advances in the understanding of it's molecular biology and therapeutics.*

**Methods:** *Various therapeutic advances in the field have been reviewed. Special focus is on emerging treatments: especially oral tyrosine kinase inhibitors which target the activity of the bcr-abl tyrosine kinase.*

**Results:** *Initially therapy revolved around early allogenic stem cell transplantation. The introduction of the oral tyrosine kinase inhibitor imatinib and other such molecules has however changed the management paradigm. The high response rates and excellent tolerance to initial therapy has tilted the balance away from allogenic stem cell transplantation.*

**Conclusions:** *Better understanding of the molecular basis of disease has resulted in the availability of a plethora of agents whose potential has yet to be fully explored. Treatment paradigms in children are in a state of flux : especially relating to the role and timing of the stem cell transplant and its integration with imatinib and other therapies.*

**Keywords:** *Chronic Myeloid Leukemia, imatinib, children, dasatinib, transplantation*
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## Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by increased proliferation of myeloid cell lines. The disease evolves through various phases: chronic phase, accelerated phase and blast crisis which can be myeloid, lymphoid, erythroid or undifferentiated. It is characterized by a cytogenetic abnormality (present at the level of the hemopoietic stem cell) consisting of a reciprocal translocation between the long arms of chromosomes 22 and 9; t(9;22): the Philadelphia chromosome. This results in relocation of the oncogene abl from the long arm of chromosome 9 to the long arm of chromosome 22 in the bcr region. The resulting bcr/abl fusion gene encodes a chimeric protein with strong tyrosine kinase activity. The expression of this protein leads to the development of CML [1].

The disease was initially described in Europe in the 1840s. In the 20th century significant advances were made regarding the molecular basis of disease. The Philadelphia chromosome was discovered in 1960. The breakpoint cluster region on chromosome 22 was discovered in 1984 as was the bcr-abl fusion gene in 1986. This work laid the foundation for the discovery of imatinib mesylate - a tyrosine kinase inhibitor (TKI) [2].

Treatment of CML has evolved over time. Early treatment modalities included arsenic, radiotherapy and busulfan. This was followed by hydroxyurea and subsequently interferons and allogenic stem cell transplantation [2].

The introduction of imatinib and other such molecules has however changed the management paradigm. The high response rates and excellent tolerance to initial therapy has tilted the balance away from allogenic stem cell transplantation.

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Better understanding of the molecular basis of disease has resulted in the availability of a plethora of agents whose potential has yet to be explored. Thus treatment paradigms in children are in a state of flux and especially relate to the role and timing of the stem cell transplant and its integration with imatinib and other therapies.

**Clinical features**

CML remains a rare disease in children accounting for 2-3% of all childhood leukemias while in adults it constitutes approximately 20% of all leukemias [3]. A Japanese study found that CML represented 0.2% of leukemias between 1 and 4 years of age, 2.2% between 5 and 9 years, 3.7% between 10 and 14 years, and 8.3% between 15 and 19 years [4]. Most of the children (>60%) are more than 10 years of age and in the chronic phase. Main presenting features include asthenia (45%), discomfort related to the presence of an enlarged spleen (20%), weight loss, bleeding (17.5%) and fever (10%). Priapism though rare (1%) is a rather dramatic presenting feature [3-6]. Splenomegaly represents the predominant physical sign (70%): in 40% of these patients the spleen extends >10 cm below the costal margin. Children tend to have higher leukocyte counts as compared to adults (median $242*10^9$/L v/s $12-174*10^9$/L). Pediatric CML resembles adult CML closely and most data regarding therapeutic interventions are drawn from adult studies: especially so since it is comparatively rare [3-5].

**Treatment options**

**Imatinib**

Imatinib is an oral drug which inhibits the bcr-abl gene product tyrosine kinase with high selectivity. It has dramatically reduced the yearly risk of progression from CP to advanced stages to less than 1% per year [7-10]. However, it does not cure the disease, the leukemic stem cells persist and various biological mechanisms can result in resistance [8]. Hematopoietic stem cell transplantation (HSCT) remains the only potentially curative option.

Imatinib is the best upfront treatment for CML. The IRIS study evaluated the use of imatinib in adults and showed that at a median follow-up duration of 19 months 95% of patients had achieved a complete hematologic response (CHR: which involves normalization of the blood counts and peripheral smear as well as physical findings like splenomegaly) and 74% had achieved a complete cytogenetic response (CCyR) [11]. The 7-year update showed an actuarial overall survival (OS) of 86%. Responding patients whose disease had not progressed in any way in their first 3 years of the study were extremely unlikely to relapse at a later stage and also unlikely to suffer from any late onset side effects. The risk of events

averaged 5.2% per year for the first 3 years, and only 0.9% per year for the subsequent 3 years. 57% of the original patient cohort was still in continuing CCyR taking imatinib on study according to the original protocol [12].

The drug has also been evaluated in children. The starting dose in children should be near $300mg/m^2$ ($260-340mg/m^2$ : identified as giving drug exposures similar to the 400-600mg adult dosage levels) orally once daily. In chronic phase (CP) most patients achieve normal blood counts within 3 months. Complete haematological and cytogenetic responses are achieved with a probability of 96 and 69%, respectively, after one year of treatment. Side effects occur in less than 10% of patients and include nausea, vomiting, diarrhea, skin rash, elevated liver enzymes, edema and cytopenias [13-16]. Management of neutropenia might entail use of growth factors. Severe thrombocytopenia may, however, necessitate dose reduction or a change to another agent. Drug absorption and metabolism may be affected by other concomitant medications, and possible adverse effects of drug interactions must always be excluded first. The side effect profiles are similar in children and adults. Additional concerns which have not yet been found to be of much clinical relevance include development of additional chromosomal abnormalities involving chromosomes Y, 8 and 7 in Ph-negative cells [17] and possibility of development of congestive cardiac failure which was suggested by its detection in 10 out of more than 1000 adults under treatment. However this incidence was considered to be no different than in the general population [18].

Imatinib impairs the activity of osteoblasts and osteoclasts [19-22]. These side effects may be of major concern in growing patients. It is advisable to withold pregnancy whilst the drug is being administered. Although normal pregnancies have been reported there has been a higher incidence of certain anomalies including hypospadiasis, exomphalos and defective skeletal formation [23].

**Monitoring for response**

Initially hemograms may be monitored for normalization for blood counts (achievement of complete hematological responses or CHR). This would be followed by assessment of changes in marrow metaphase cytogenetics until a patient achieves CCyR (complete cytogenetic response) and then to carry out RQ-PCR (real time quantitative reverse transcriptase polymerase chain reaction) for BCR-ABL1 transcripts to detect molecular responses [24-28]. FISH (Fluoroscent In situ hybridization techniques) may be used if RQ-PCR for BCR-ABL1 is not available [29]. Currently it is recommended that blood counts be performed at least weekly until they have

stabilized, with greater intervals thereafter. Once CHR has been documented, monitoring continues with karyotyping of at least 20 bone marrow metaphases, which is currently recommended at 3, 6, 12, and 18 months (recommendations varying between 3-6 monthly monitoring), or until CCyR has been achieved while molecular monitoring has been recommended every 3 months after attainment of CCyR [24-28].

*Defintion of imatinib failure*

The patient is defined to have imatinib failure if he /she does not achieve any of the following: some level of hematologic response after 3 months, a CHR with some level of cytogenetic response at 6 months, less than 35% of Philadelphia chromosome positive (Ph+) marrow metaphases (Partial cytogenetic response or PCyR) at 12 months or a CCyR at 18 months. The loss of CHR, CCyR or developments of kinase domain mutation insensitive to imatinib also constituted imatinib failure [29,30].

*Defintion of optimal response*

This has been defined as achieving CHR, and at least a minor CyR ( Ph+ < 65% cells ) at 3 months, at least a partial CyR (Ph+ < 35%) at 6 months, CCyR at 12 months and MMR ( major molecular response defined as a 3-log reduction in transcripts as compared to baseline) at 18 months [28,30,31].

*Role of imatinib dose escalation in case of imatinib failure*

The primary data has come from adult studies in which doses have been escalated to 600 or 800 mg/day. In a phase 2 study dasatinib (70 mg twice daily) was compared with imatinib (400 mg twice daily) in patients failing standard dose imatinib. MCyR (Major Cytogenetic Responses :defined as the sum of PCyR and CCyR) at 12 weeks were similar (36% for dasatinib vs 29% for imatinib; P = .40), but the rates of MCyR, CCyR and MMR at later time points as well as treatment failure at 15 months ( 28% v/s 82%) all favored dasatinib [32]. In another such study after a median follow-up of 5 years, 30% maintained a CCyR while still receiving imatinib [33]. Thus imatinib dose escalation is feasible and can provide durable responses. However, caution is warranted in cases who fail to achieve any response to standard dose imatinib or those progressing on 600 mg per day of imatinib.

**Dasatinib**

This multikinase inhibitor binds to Bcr-Abl in its open/active and closed/ inactive conformations as well as the Src family kinases (SFK) and is useful in imatinib resistant/intolerant cases [34]. The START-C trial evaluated dasatinib in 288 imatinib-resistant patients.

After a median follow-up of 15 months, 87% of patients had achieved a new complete hematologic responses (CHR) and 56% had achieved a new MCyR with an estimated 90% PFS [35]. Encouraging data is also emerging from recently conducted studies in children [36].

**Nilotinib**

Like imatinib, nilotinib targets the inactive conformation of the Abl enzyme, yet has a higher affinity for the kinase and is useful against imatinib-resistant mutations [37]. In a study of 220 imatinib-resistant CP-CML adult patients a 56% MCyR rate and a 41%CCyR rate after a minimum follow-up of 19 months. More than 75% patients maintained their MCyR at 24 months with a reported PFS of 50% to 60% [38]. Patients with T315I mutations are resistant to TKI's. Those with Y253H, E255K/V, F359V/C mutations may be more susceptible to dasatinib while those with T315A and V299L mutations may benefit from nilotinib [39-42].

Newer TKI's like bosutinib and INNO - 406 are being developed. Patients with the T315I mutations are unlikely to benefit from TKI's and various drugs like homoharringtonine, aurora kinase inhibitors and switch pocket inhibitors have demonstrated promising activity and are in various stages of trial and evaluation [43-47].

*The predictive role of molecular markers*

The achievement of MMR by 18 months represents a milestone wherein the risk of progression including loss of CCR is extremely low [48]. Achievement of CCyR without MMR can be unstable especially in late chronic phase as in the GIMEMA study where the annual risk of losing CCR once established was 7.5% per year in years 1 and 2 and 4.5% per year in years 3 and 4 [49]. In patients on dasatinib and nilotinib the BCR-ABL level measured at 3 months was highly predictive of MMR by 24 months. Patients with a BCR-ABL value of <1.0% IS (international scale) had an 86% probability of an MMR by 24 months. Those with values of 1.0% to 10% IS or >10% IS had a significantly lower probability of MMR at 55% and 4%, respectively. Patients in minor CyR or CHR at 12 months had a projected 1-year progression rate of 17% compared with 3% for those with MCyR. at 12 months and constituted a population at high risk of failure [50,51]. These pieces of evidence might prove to be of benefit while considering further treatment strategies in such patients.

**Stem Cell Transplantation**

For the rare patient with a genetically identical twin upfront transplantation is the treatment of choice since the

risk of transplant-related mortality is extremely low with syngeneic donors. Stem cell transplantation used to be the treatment of choice in children before the introduction of imatinib. Some of the largest studies have shown results to be similar to those obtained in young adults [52-55]. These studies have reported a 3 year overall survival (OS) and leukemia-free survival (LFS) rates in the range of 66% and 55% respectively. For the children in first chronic phase (CP1) who underwent transplantation from HLA-identical siblings, OS, LFS and treatment related mortality rates (TRM) were 75%, 63% and 20% respectively. Results were worse in patients who underwent SCT in CP1 from VUD (voluntary unmatched donors), 3-year OS, LFS and TRM rates were 65%, 56% and 35%. Moderate to severe GVHD occurs in 37% cases undergoing transplantation from HLA identical siblings and in 53% cases undergoing VUD transplants. This was despite using T cell depletion techniques in almost 61% VUD's and 14% of matched sibling donors. Outcomes were superior in children who underwent transplant within 6 months of diagnosis as compared to those who underwent it later [52].

The trial CML paeds 1 achieved better results in patients transplanted from HLA identical family donors with a 5 year OS of 87±11% but OS was 52±9% (for HLA-matched VUD) and 45±16% (for HLA-mismatched VUD) respectively. The OS was 74±9%, if the procedure was performed within 6 months after diagnosis, and 62±15% if performed after 6-12 months or later than 12 months after diagnosis [55].

The CML-paeds 2 trial aims at starting children on imatinib and monitoring for disease response. Non responders are taken up for transplant immediately. However responders are also transplanted at 2 years from start of therapy [56].

**Advanced stages of disease (accelerated phase - AP, blast crisis - BC)**

In advanced stages children should be treated with higher doses of imatinib: $400mg/m^2$ (maximum absolute dose 600 mg) in AP, and $500mg/m^2$ (maximum absolute dose 800mg) in BC, respectively [28,57].

Adult studies suggest that dasatinib has good efficacy in imatinib resistant / intolerant patients with advanced stages/ BC [58]. The presence of BC suggests that there is need for a much more aggressive initial strategy. For patients in lymphoid BC combining imatinib with standard ALL treatment may be the best initial approach. Once remission is achieved maintenance therapy together with a TKI can then be continued. Neuroprophylaxis is advisable. For patients presenting in myeloid BC the combined use of a TKI with AML therapy may be the best approach. In both lymphoid and myeloid BC the

probability of relapse is high and patients achieving CP should be taken up for transplantation if feasible [28,55]. It is logical to continue the use of a TKI after allogenic transplantation but no controlled series have been reported. [28] Allogenic stem cell transplantation is still the best modality with OS and leukemia free survival (LFS) of 35% and 34% at 3 years [52].

**Conclusions**

At present imatinib is the upfront therapy of choice. Other TKI's like dasatinib and nilotinib have a emerging role in resistant / intolerant cases. Pediatric data is at present scarce and is evolving. Newer drugs also are on the anvil. Many of the treatment strategies are extrapolated from adult studies. Allogenic transplants are the only curative option. HLA matched sibling transplants are preferable. However transplants are associated with much higher rates of treatment related morbidity and mortality. While definite recommendations can only be made once the data matures, the general trend seems to be to use transplants as treatment strategies after failure of oral therapy or upfront in cases of advanced disease especially in blast crisis.

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