Review Article

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Paediatric chronic myeloid leukaemia: Is it really a different disease?

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Paediatric chronic myeloid leukaemia (CML) has biological and clinical differences from adult CML. Management of paediatric CML presents unique challenges in growing children, and there are no specific guidelines for paediatric CML. This review focusses on the clinical characteristics, diagnostic issues and management of paediatric CML. Major studies that provide the basis of managing paediatric CML are summerized here. Studies conducted on adult CML patients were used to guide the management of places where studies were lacking in paediatric CML. Recently, dasatinib and nilotinib have been approved for treatment of paediatric CML, and their role has been discussed in the current management perspective. Allogeneic transplant, fertility and vaccination in paediatric CML, have also been discussed.

Key words Chronic myeloid leukaemia - dasatinib - fertility and chronic myeloid leukaemia - imatinib - nilotinib - treatment-free remission

Introduction

Chronic myeloid leukaemia (CML) is characterized by translocation between chromosomes 9 and 22, resulting in the formation of Philadelphia (Ph) chromosome. This translocation generates breakpoint cluster region (BCR)-ABL1 chimera messenger RNA and results in leukaemic cells with growth advantages[1]. CML usually presents in the age group of 45-55 years. It is a triphasic disease with most cases (85%) diagnosed in CML-chronic phase (CP) with common symptoms being fatigue, weight loss, abdominal fullness, bleeding, purpura, splenomegaly, leucocytosis, anaemia and thrombocytosis[2]. The natural history of CML-CP is progression to accelerated phase (AP) and blast crisis (BC) in 3-5 years[3]. Currently, tyrosine kinase inhibitors (TKIs) have revolutionized the treatment and are the mainstay of treatment. Before imatinib, patients had a dismal outcome; however, with availability of TKI, it has improved over the years. Survival data from Southern-Eastern Europe and United States of America Surveillance, Epidemiology and End Results (SEER) showed significantly (67%) lower risk of death within two-year follow up when pre-TKI period was compared with post-TKI period[4].

Paediatric CML is rare compared to adult CML and accounts for approximately 2-3 per cent of cases of newly diagnosed paediatric leukaemia. Age-adjusted SEER cancer incidence rate from 2010 to 2014 for the age group of 0-14 yr was 1.4 per 1,000,000 whereas for the age group 0-19 yr it was 2.1 per 1,000,000[5]. Below the age of one year, CML is extremely rare. In India, CML is usually seen in children older than 12 years[6]. The National Cancer Registry Programme of India registers all childhood leukaemia cases in a

single group; hence, there is no separate data collection for paediatric CML[7].

There are significant differences in paediatric and adult CML. Biologically, in adult CML, there is a single breakpoint cluster within the first centromeric 1.5 kb of the BCR, whereas in paediatric CML, there is a bimodal breakpoint distribution which is similar to adult Ph+ acute lymphoblastic leukaemia (ALL) with M-BCR rearrangement[8]. The clinical presentation of paediatric CML differs from adult CML. The median white blood cell (WBC) count at baseline in adult CML ranges from 80 to 150×10^9/l; however, in childhood CML, the median WBC count was 250×10^9/l in a study of 200 patients with a median age of 11.6 years[9]. Data analysis from randomized CML IV study showed that adolescents and young adults had clinical features suggestive of aggressive disease with larger spleen size, higher WBC count, higher percentage of peripheral blasts, and lower haemoglobin compared to other age groups. At three months, higher rate of BCR-ABL transcript level of more than 10 per cent on international scale was seen, although there were no differences in cytogenetic remission, molecular remission and survival with respect to other groups[10]. A retrospective analysis found that adolescent and young adults had inferior complete cytogenetic response (CCyR), major molecular response and complete molecular response compared to older patients although there were no differences in survival[11]. The proportion of patients with CML-AP and CML-BC in paediatric CML patients have been 1.9 and 4.4 per cent in CML-Paed-II Trial and 6 and 2 per cent in I-CML-Ped Study, respectively[12,13]. In adult CML, in a large series of patients, CML-AP was 2 per cent whereas CML-BC was 0.3 per cent[14]. Sokal score, Euro and European Treatment and Outcome Study scores that predict outcome in adult patients with CML do not predict response and outcome in paediatric CML[15]. It appears that there are differences in paediatric and adult CML, but the impact on treatment outcomes is not clear as yet.

In view of the above-mentioned difference, there is a need to treat it as a separate entity. At present, data in paediatric CML are emerging and there is lack of clear guidelines for paediatric CML. Paediatric patients due to growth period are susceptible to unique side effects of TKI and are also prone to long-term toxicities. Due to long life span of paediatric patients, treatment targeting cure appears to be the aim rather than suppression of the disease. At present, we do not know if TKI can be stopped in paediatric patients although it appears to be feasible in selected patients. Recently, dasatinib and nilotinib have been approved in paediatric patients by the Food and Drug Administration (FDA)[16,17]. The present review addresses paediatric CML-specific issues, and recent development in this area.

When to suspect CML in children

Clinical presentation of splenomegaly with leucocytosis in a relatively preserved child raises the suspicion of CML. Patients usually present with malaise, fatigue, fever, night sweats, weakness and symptoms due to splenomegaly and bleeding because of platelet dysfunction. Occasionally, a child can present with headache, visual disturbances and priapism due to hyper-leucocytosis. Children with AP present with above symptoms as well as lymphadenopathy, cutaneous involvement, rapid progression of systemic symptoms and splenomegaly. CML-BC mimics clinical picture of acute leukaemia[18].

In I-CML-Ped Study which analyzed 150 patients, the median age at diagnosis was 11.6 yr with male preponderance (59%)[13]. The median leucocyte count was 250×10^9/l and splenomegaly was seen in 76 per cent of patients with a median size of 8 cm below the subcostal margin. As per Sokal risk score, 55 per cent were at high-risk, 33 per cent intermediate and 13 per cent at low-risk. In India, a retrospective study of 51 patients reported a median age of 16 yr with male preponderance with presenting features of fatigue, fever and splenomegaly[19]; in this study, the median leucocyte count was 170×10^9/l and splenomegaly was seen in 90 per cent, Sokal risk score was high in 32 per cent, intermediate in 21 per cent and low in 14 per cent. Similar clinical features were reported by Ganta *et al*[20] in a retrospective study of 48 patients.

Differential diagnosis

Diseases that can closely mimic CML-CP are leukemoid reaction, juvenile myelomonocytic leukaemia (JMML), atypical CML and other myeloproliferative disorders. Leukemoid reaction is due to infections characterized by high leucocyte count with neutrophilia and left shift. It can be distinguished from CML-CP by the presence of toxic granulations, high leucocyte alkaline phosphatase, lack of myelocyte bulge and focus of infection. Cytogenetic or molecular tests can differentiate it from CML but is not required usually. JMML has a distinct set of diagnostic criteria[21]. JMML is clinically characterized by hepatosplenomegaly, lymphadenopathy, anaemia,

fever and skin rash. Ph chromosome is absent in JMML. Atypical CML and other myeloproliferative disorders are rare in children, and these can be distinguished by their diagnostic criteria and absence of Ph chromosome and BCR-ABL1[21]. CML lymphoid BC can be difficult to distinguish from Ph+ ALL. Marked splenomegaly, basophilia, myelocyte bulge and p210 fusion gene (p190 in Ph+ ALL) distinguish CML lymphoid BC with Ph+ ALL. In CML lymphoid BC, Ph chromosome will be in the lymphoblasts and in the neutrophils, whereas in Ph+ ALL, it is restricted to the lymphoid cells[22].

Diagnosis

Peripheral smear shows leucocytosis and differential leucocyte count shows all cells of granulocytic series with peaks in neutrophils, myelocytes and metamyelocytes. Absolute basophilia is seen in all patients and absolute eosinophilia is seen in 90 per cent patients. Absolute lymphocytosis is also often seen[23]. Most of the patients have normal platelet counts or thrombocytosis, whereas thrombocytopenia is seen in <5.5 per cent of patients[24]. Bone marrow aspiration and biopsy shows granulocytic hyperplasia along with maturation pattern similar to peripheral smear. Blasts are <5 per cent of nucleated marrow cells[25]. Dwarf megakaryocytes which are smaller than normal megakaryocytes with hypolobulated nuclei are characteristic findings. Myelofibrosis has been reported to be 26 per cent in a large multicenter study[26] whereas the range is from 15 to 65 per cent depending on the method of diagnosis in adult CML.

Ph chromosome is the hallmark of CML which can be detected by karyotyping, fluorescent *in situ* hybridization (FISH) and reverse transcriptase (RT)-PCR. In adults, t(9;22) translocation is present in 95 per cent of patients. The remaining five per cent have variant translocations involving a third or even a fourth chromosome in addition to chromosome 9 and 22[27]. In these cases, BCR-ABL1 can be detected by RT-PCR or FISH.

At baseline, complete blood count, peripheral blood smear, bone marrow aspiration and biopsy, cytogenetics and RT-PCR for BCR-ABL1 need to be done. Quantitative RT-PCR at baseline is not required. FISH should be done if marrow cytogenetics is negative[2]. Immunophenotyping by flow cytometry is suggested in CML-BC for lineage determination[28]. Tyrosine kinase domain (TKD) mutation analysis at diagnosis is recommended in CML-AP/BC and not at baseline[29].

Management

Initiation of treatment

Patients are started on allopurinol, oral hydration and hydroxyurea till the diagnosis is established. Despite high leucocyte counts, CML-CP is considered as low-risk for tumour lysis syndrome[30]. Leukapheresis is recommended if patient has priapism, pulmonary infiltrates and severe retinopathy[29]. Imatinib is started after the establishment of diagnosis.

Imatinib: TKIs are the first line of treatment in CML-CP in paediatric CML. Imatinib is currently the standard of care in first line. CML-PAED-II study is the largest phase 3 study which evaluated the efficacy of imatinib as frontline in children and adolescent[12]. Imatinib was administered 260-300 mg/m^2 (maximum dose 400 mg once daily) in 140 patients with CML-CP. Eighty nine per cent patients achieved complete haematological response (CHR) of evaluable 121 patients at three months. At 12 months, major cytogenetic response (MCyR) was achieved in 80 per cent, CCyR was achieved in 63 per cent, major molecular remission (MMR) was achieved in 46 per cent of patients at 12 months in a cohort of 140 patients, at an average of 10.8 months. At 18 months, 97 per cent of patients were event free[12]. Similar CHR has been reported in other paediatric CML studies[13,20,31,32]. MCyR at 12 months ranged from 19 to 96 per cent and MMR at 12 months ranged from 12 to 82 per cent[20,31-33]. The differences have been attributed to dose and compliance of imatinib[12].

Imatinib is available in the strength of 100 and 400 mg. Oral bioavailability is 98.3 per cent with a half life ($t_{1/2}$) of 19.3 h in steady state enabling once daily oral administration[34]. Imatinib due to irritant property is preferably given with a glass of water in sitting position. It can be given after breakfast or before going to sleep to mitigate nausea[29]. The recommended dose of imatinib in CML-CP is 260-340 mg/m^2 (maximum absolute dose 400 mg)[35]. Imatinib is rounded off to the nearest 50 as 100 mg tablets are scored. In a study of 44 patients using a dose of 260 mg/m^2, CHR at three months was 86 per cent, CyCR and MMR at 12 months were 61 and 31 per cent, respectively; estimated progression-free survival (PFS) at 36 months was 98 per cent[32]. Similar figures using a dose range of 260-300 mg/m^2 were achieved[12]. At a dose of 340 mg/m^2, CyCR and MMR at 12 months were reported to be 96 and 67 per cent, respectively[33]. The superior results have been attributed to higher

dose of imatinib. However, the impact of higher dose of imatinib on survival in paediatric CML-CP is not known at present.

Imatinib toxicity: Imatinib is tolerated well in paediatric CML. In the largest cohort of 148 patients treated with imatinib, grade ¾ anaemia, neutropenia and thrombocytopenia were seen in 10.9, 14.1 and 3.2 per cent patients, respectively. All grades of skin toxicity and oedema were seen in 17.6 and 4.9 per cent patients, respectively. Nausea (25%), vomiting (17%), diarrhoea (9.4%) and hepatotoxicity (7.4%) were the common gastrointestinal toxicity with grade 3 hepatoxicity occurring in one patient only. Muscle cramps (22.3%) and bone and joint pain (5.1%) were the common musculoskeletal complaints. Growth deceleration was seen in 47.2 per cent out of which 16.6 per cent had grade 3 growth deceleration, which was observed in pre-pubertal children[12]. Other studies have also demonstrated growth inhibition primarily in pre-pubertal children[36,37]. Catch-up growth occurs in puberty, but at present, it is not known if it is adequate to attain the expected adult height[38]. Imatinib has been reported to cause bone resorption, resulting in a decrease in chronological bone mineral density[39]. Imatinib dysregulates vitamin D, calcium and phosphate metabolism. In a study of 17 patients with paediatric CML on imatinib, four had hypocalcaemia, three had hypophosphatemia and nine patients developed 25-hydroxyvitamin D3 deficiency and secondary hyperparathyroidism[40]. In another study, the authors recommend monitoring of calcium, phosphorus, parathyroid hormone and vitamin D levels at six weeks of starting TKI followed by every six months[38]. Transient thyroid dysfunction has been reported in 74 per cent of patients in a study of 39 patients with adult CML. However, only three patients required therapy and none required cessation of TKI[41]. In paediatric CML, monitoring of thyroid-stimulating hormone and T4 at 4-6 wk after initiation of therapy followed by 6-12 monthly follow up is recommended[38]. Impact of imatinib on adrenal functions in paediatric CML patients is not known.

Common side effects can be managed with supportive care and counselling. Myelosuppression is usually seen in the first six weeks[29]. Myelosuppression can be due to drug toxicity or disease progression. In a retrospective study of 48 paediatric CML patients, those who were compliant with >90 per cent of the drug schedule in first six months attained a significantly higher CCyR (79 vs 5%) versus those who were compliant with ≤90 per cent of the drug schedule[20]. As this study establishes that treatment interruptions are detrimental to outcome, it is suggested to continue imatinib unless grade 3 or 4 toxicities occur which will warrant interruption. Anaemia is managed by transfusion or erythropoietin. Neutropenia is managed by administering granulocyte-colony stimulating factor (G-CSF) and imatinib can be continued depending on clinician's judgement. Imatinib cessation is recommended when neutrophil count is $<1\times10^9$/l and imatinib is restarted when neutrophils $>1\times10^9$/l. If duration of neutropenia is less than two weeks, imatinib is started at full dose, and if duration is more than two weeks, 20 per cent dose reduction is needed[29]. Imatinib should be stopped if platelet count is $<50\times10^9$/l; in case of recurrent thrombocytopenia, 20 per cent dose reduction is suggested[29].

Nausea is common initially after starting imatinib; it is usually managed by giving after going to bed or use of antiemetics. Facial puffiness and oedema can be managed by diuretics. Bone pain is usually observed in the initial part of treatment and is treated with non-steroidal anti-inflammatory agents. Muscle cramps, skin rash and diarrhoea are managed with supportive care[29]. Patients who develop growth retardation can be administered growth hormone if indicated. Problems of bone, mineral metabolism and thyroid disorders should be treated if clinically indicated. Further studies are required to evaluate endocrinological disorders on patients who are on imatinib and whether imatinib cessation is required.

Dasatinib: Dasatinib has been approved for the treatment for CML-CP patients older than one year. In a phase 2, open-label, non-randomized prospective trial which included 61 newly diagnosed CML-CP patients, at 12 months, CCyR and MMR attained were 92 and 52 per cent respectively[42]. Dose of dasatinib tablet was 60 mg/m^2 and powder for oral suspension was 72 mg/m^2. Compared to imatinib, the responses were earlier and deeper; however, it is to be noted that imatinib at dose of 340 mg/m^2 achieved similar responses[12,32,39]. In adult CML-CP, dasatinib at five years achieved improved MMR (76 vs 64%, P=0.0022) and molecular response with 4.5-log reduction (42 vs 33%, P=0.021), but five-year estimated overall survival (OS) [91 vs 90%, hazard ratio (HR), 1.01; 95% confidence interval (CI), 0.58-1.73] and five-year PFS (85 vs 86%, HR, 1.06; 95% CI, 0.68-1.66) when compared to imatinib were not significantly different[43]. In paediatric CML-CP, long-term data are required to establish the impact of early and deeper response achieved by dasatinib

on survival. Dasatinib-related adverse effects such as pleural effusion, pericardial effusion and pulmonary artery hypertension, which occur in adults, did not occur in children[42]. Myalgia, fatigue, rash, diarrhoea and impairment of bone and growth development were observed[42].

Nilotinib: Nilotinib is approved in paediatric CML-CP in children older than one year at a dose of 230 mg/m^2 twice daily. Approval was based on the basis of two single-arm phase 2 trials CAMN107A2120 (NCT01077544) and CAMN107A2203 (NCT01844765)[44]. In 25 patients with newly diagnosed Ph chromosome-positive CML-CP, the major molecular response was achieved in 15 patients (60.0%) at 12 cycles. Adverse effects of nilotinib were similar to adult patients *viz*. hyperbilirubinaemia, thrombocytopenia, rash, neutropenia, liver enzymes elevation, QTc prolongation, nausea and vomiting[44]. Bosutinib, ponatinib and radotinib are not approved at present in paediatric CML-CP.

Monitoring and response assessment

At present, there are no separate guidelines for paediatric CML. European Leukemia Net (ELN) guidelines or National Comprehensive Cancer Network (NCCN) guidelines for adult CML are used as guiding principle[45,46]. Response is monitored three monthly with peripheral blood quantitative PCR for BCR-ABL[9,45]. NCCN recommends three monthly peripheral blood BCR-ABL1 and cytogenetics in case of failure to achieve milestones or loss of response[46]. Response is classified into optimal, warning and failure. In optimal response, the TKI needs to be continued; in warning, the patient requires close monitoring and in failure of therapy, TKI should be changed[45]. In case of failure of therapy, TKD mutation analysis should be done. If TKD mutation is sensitive to dasatinib or nilotinib, appropriate drug is selected. Response assessment in the NCCN guidelines is stringent whereas ELN guidelines are less stringent as these classify responses in warning category also, because cut-offs can fluctuate.

Data for dasatinib and nilotinib as the second-line TKI are limited. In a phase 2 study, which had 29 patients of CML-CP intolerant/resistant to imatinib, dasatinib was administered 60 mg/m^2. At 12 months, MMR was in 41 per cent and CMR was in seven per cent, whereas at 24 months, it was 55 and 17 per cent, respectively. The median PFS and OS were not reached[42]. Nilotinib was studied in two single-arm trials [CAMN107A2120 (NCT01077544) and CAMN107A2203 (NCT01844765)] in paediatric patients with Ph chromosome-positive CML-CP resistant or intolerant to imatinib or dasatinib[44]. Nilotinib was administered at a dose of 230 mg/m^2 twice daily, rounded to the nearest 50 mg dose in 28 day treatment cycles. In 44 patients with resistant or intolerant Ph chromosome-positive CML-CP, MMR was achieved in 18 patients (40.9%) at 12 cycles[44]. A retrospective study evaluated the sequential use of second-generation TKI in 31 patients due to poor response or intolerance to imatinib[47]. After switching to second-generation TKI, responses were improved in 63 per cent and stable in 37 per cent[47]. All patients achieved or maintained CHR including to CML-blastic phase (BP) patients[47]. In view of good responses to second-line TKI, we suggest second-generation TKI for those who have suboptimal response to imatinib. In case of suboptimal response or intolerance to second-generation TKI, patient should be considered for haematopoietic stem cell transplant (HSCT) or enrolled in clinical trials[9]. In case, TKD T315I mutation is detected, either HSCT should be considered or the patient should be enrolled in a clinical trial[9].

How long to continue imatinib?

Imatinib discontinuation is feasible in adult CML-CP patients. A meta-analysis of 15 cohort studies of imatinib cessation in patients with undetectable BCR-ABL transcript level including 509 patients showed that weighted mean molecular relapse was seen in 51 per cent of patients and at six months it was 41 per cent. Eighty per cent of relapses occurred in the first six months. At the end of two years, all patients were alive and one patient progressed to BC[48]. There are recommendations for selecting patients for imatinib discontinuation in adult CML[49,50]. In paediatric CML-CP patients, a series of six patients has been reported, who discontinued imatinib themselves as they attained molecular remission. Subsequently, all of them lost MMR warranting reintroduction of TKI[51]. In a case series of three patients, this approach was shown to be feasible in selected patients with long duration of molecular response[52]. International Berlin-Frankfurt-Münster (IBFM) CML study group has made recommendations in situations where patients discontinue imatinib themselves or imatinib needs to be stopped due to unacceptable toxicity, for stopping imatinib in paediatric CML patients who have achieved and maintained complete molecular response for more than two years[53]. Although the need to stop imatinib in paediatric CML is compelling and

desirable, at present, we do not recommend stopping imatinib outside clinical trial in paediatric CML-CP patients in view of insufficient data.

Chronic myeloid leukaemia (CML)-accelerated phase (AP)

In adults, ELN has defined as "CML-AP blasts in the blood or marrow of 15-29 per cent, or blasts plus promyelocytes in the blood or marrow >30 per cent, with blasts <30 per cent, basophils in the blood ≥20 per cent, persistent thrombocytopenia (<100×10^9/l) unrelated to therapy, clonal chromosome abnormalities in Ph+ cells major route on treatment"[45]. The World Health Organization (WHO) defines CML-AP if anyone of the following criteria is fulfilled: "persistent or increasing WBC (>10×10^9/l) unresponsive to therapy, persistent or increasing splenomegaly unresponsive to therapy, persistent thrombocytosis (>1000×10^9/l) unresponsive to therapy, persistent thrombocytopenia (100×10^9/l) unrelated to therapy, 20 per cent or more basophils in the peripheral blood, 10-19 per cent blasts in the peripheral blood and/or bone marrow, additional clonal chromosomal abnormalities in Ph+ cells at diagnosis that include 'major route' abnormalities (second Ph, trisomy 8, isochromosome 17q, trisomy19), complex karyotype, or abnormalities of 3q26.2 and any new clonal chromosomal abnormality in Ph+ cells that occurs during therapy"[21]. Upfront CML-AP in paediatric CML is rare, 1.9 per cent in the largest study of paediatric CML[12]. In a retrospective study, in 50 adult patients with CML-AP treated with TKI as initial therapy at 12 months, CCyR and MMR were achieved in 63 and 50 per cent of patients, respectively[54]. Three year event-free survival (EFS) and OS were 86 and 89 per cent, respectively. The outcomes were similar to comparison cohort of CML-CP patients treated in the same institution. Patients who received second-generation TKI had higher CCyR (90 vs 80%) and MMR (76 vs 63%), but there was no significant difference in EFS and OS[54]. In view of these data in adults, we suggest initiating TKI as first-line therapy in CML-AP. In case of inadequate response to TKI, HSCT should be considered.

Chronic myeloid leukaemia (CML)-blastic phase (BP)

CML-BP is defined by ELN as blasts in the blood or marrow ≥30 per cent or extramedullary proliferation apart from spleen[45]. The WHO defines CML-BP blasts in the blood or marrow ≥20 per cent, extramedullary blast proliferation, apart from spleen; large foci or clusters of blasts in the bone marrow biopsy[45]. In adult CML advanced phase patients, The Center for International Blood and Marrow Transplant Research (CIBMTR) Study that compared outcomes of those who received imatinib before transplant and those who did not found no significant difference in OS at three years (36 vs 34%, P=0.61), leukaemia-free survival, treatment-related mortality and relapse[55]. Similarly, another retrospective study compared patients who received imatinib with a cohort of patients who did not receive imatinib before allogeneic HSCT (AHSCT)[56]. They did not find any difference in OS, disease-free survival, relapse and treatment-related mortality in the two groups. However, they found that patients who achieved CCyR or MCyR on imatinib had significantly lesser hazard for mortality. Suboptimal response to imatinib was a predictive factor of poor outcome, reflecting aggressive biology of the disease[56]. In imatinib era, a small retrospective study of five paediatric patients in CML-BC used imatinib before AHSCT, followed by imatinib for two-year post-transplant starting from day 100. All patients were in haematological and cytogenetic remission at the time of transplant. All patients were in molecular remission at an average follow up of 38 months[57]. More data are required to devise an optimal treatment for paediatric CML-BP. Till then, TKI followed by AHSCT and maintenance TKI appears to be a reasonable approach.

Allogeneic haematopoietic stem cell transplant (AHSCT) in CML

Before imatinib, AHSCT was the standard of care. Five-year survival in CML-CP1 ranged from 59.3 to 87 per cent in a large series of patients[58-60]. In the current TKI era, it is estimated that five-year survival will be approximately 94 per cent[12]. In view of immediate and long-term complications of AHSCT, TKIs are preferred as the first-line treatment. In case of suboptimal response to imatinib, the second-line TKI dasatinib or nilotinib should be used depending on TKD mutation testing as well as donor search should be done. When there is suboptimal response to second-generation TKI or T3151 mutation, AHSCT should be done. In CML-AP, suboptimal response to first-line TKI requires evaluation for transplant. CML-BC requires upfront AHSCT.

Fertility and CML

At present, imatinib is continued indefinitely, so it is inevitable that many patients will reach child-bearing age. In a study of 48 male patients of CML-CP, imatinib

crossed blood-testis barrier and resulted in reduced sperm density, sperm count, survival rates and activity[61]. Sex hormone levels and structure of reproductive organs were not affected; however, 19 patients were diagnosed with hydrocele[61]. No increased risk of malformations or increased abortion has been noted in the female partners of more than 200 male patients who were on imatinib[62]. Dasatinib also appears to be safe in men. Of the 66 reported pregnancy outcomes of female partners of men treated with dasatinib, there were only two abortions and one case of syndactyly[62].

In the largest series of female patients taking imatinib, with known outcome of 210 pregnancies, 60 per cent were alive and healthy infants, 20 per cent elective termination, seven per cent foetal abnormality and 11 per cent spontaneous abortion[63]. In another study, 56 female patients were reported to be pregnant while taking dasatinib, of when 26 patients had abortion, 11 had malformations and the rest were uneventful[62]. Fifty cases of pregnancy while taking nilotinib were reported, of which three had malformation[62].

In view of above data, female partners of male patients on TKI are not at risk for pregnancy-related complications. TKI should be continued in male patients. For female patients, contraception should be planned during TKI. Pregnancy can be planned when the patient is in major molecular remission for more than two years[63]. For patients who become pregnant during treatment, individualized decision after discussing with patient and obstetrician should be done. TKI should be stopped and patient switched to interferon in second and third trimesters. If situation warrants that TKI should be continued, nilotinib appears to be the safest[63].

Vaccination

Literature regarding vaccination is scarce and there are no guidelines. Practically, this problem does not arise often because majority of vaccines recommended by Indian Academy of Pediatricians are completed by five years whereas CML is rare in this age group[9,64]. All killed vaccines can be given during treatment although their efficacy may be less. Live vaccines are not advised although patients who are in deep molecular response, a window period for vaccination, can be created by interrupting TKI[9].

To conclude, there are pertinent biological differences between adult and paediatric CML. Overall, the treatment is same except special consideration of growth, endocrinological dysfunction, long-term TKI toxicities, vaccination and fertility issues in adolescent and young adult patients. Treatment-free remission though well established in adults at present is not applicable in paediatric CML.

Future considerations

Endocrinological effects of imatinib need to be investigated. In future, studies are needed to establish the safety and efficacy of imatinib cessation. With the approval of second-generation TKIs which are more effective than imatinib, the question arises if these should be used in first line. Upfront second-generation TKI can achieve quicker and deeper response in paediatric CML, which can lead to treatment-free remission. Achieving treatment-free remission appears to be a more realistic and desirable goal in children than adults. Studies are required to answer it. More stringent and intense protocol for adherence and response monitoring can be explored in future to improve the outcome in paediatric CML. Long-term follow up of second-generation TKI is required as it appears that paediatric patients of CML have side effects of TKI which are different from adults. The role of AHSCT versus second-generation TKI and post-AHSCT maintenance needs to be defined. ICMLPed (NCT01281735) Study will be completed in 2020 which will describe baseline characteristics, prognostic factors, prognostic scores and long-term outcome of paediatric CML. Finally, in view of the rarity of paediatric CML, an international collaboration with inclusion of developing countries is required.

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