

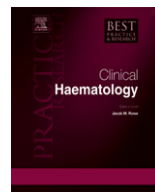


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CML in pregnancy and childhood

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With the improved survivals offered by the tyrosine kinase inhibitors has come the necessity to address issues relating to quality of life and one such area is that of fertility and parenting. Animal data suggest that imatinib at standard dosages is unlikely to impair fertility in either adult males or females but human data remain limited. Children born to men who are actively taking imatinib at the time of conception appear healthy and current advice is not to discontinue treatment. In contrast the data relating to children born to women exposed to imatinib during pregnancy are less encouraging. Although numbers are small there has been a disturbing cluster of rare congenital malformations such that imatinib cannot be safely recommended, particularly during the period of organogenesis.

The appropriate management of children with CML has also been radically changed by the advent of imatinib. The features of the disease at presentation, the natural history and the response to therapy seem to be identical in children to that seen in adults. Now that imatinib has been in clinical use for almost ten years without severe long-term side effects, most physicians are now comfortable advising a trial of imatinib prior to consideration of transplant. Data relating to the efficacy and safety of second generation tyrosine kinase inhibitors in childhood is entirely absent and transplant remains the first choice for patients failing imatinib and perhaps also for young patients with sub-optimal responses.

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The introduction of the tyrosine kinase inhibitors (TKI) into clinical practice has changed the prognosis of CML so dramatically that patients diagnosed in the chronic phase can reasonably expect

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many years of excellent disease control and good quality of life. This transformation from a disease that is almost inevitably fatal to that of a chronic condition with perhaps normal life expectancy presents particular issues for at least two distinct patient populations. The first is those individuals of child-bearing age who wish to manage their expectations of parenting and family life within the treatment of their leukaemia. The other group is children and adolescents for whom the term 'life-long' treatment has very real meaning. This chapter seeks to address these two populations and provide some guidance as to appropriate management.

CML and pregnancy

Introduction

The improved outcome of CML has resulted in the ability to parent children becoming an increasingly pressing desire for many patients (women and men) of child-bearing age who have not completed their families. Physicians are not infrequently being asked for advice regarding the need for, and/or the appropriateness of, stopping treatment in order to conceive. For obvious reasons, the data relating to the safety of the TKI before, during and after gestation remains quite limited. An international registry of pregnancy outcome has recently been established by Novartis to collect the outcomes of pregnancies in women who have been exposed to imatinib and nilotinib, but some years may elapse before further data are available. In the meantime any recommendations regarding the management of CML in pregnancy must be tempered by this lack of information.

In general many patients diagnosed with haematological malignancies and treated with targeted molecules and/or conventional combination chemotherapy can expect prolonged remission and in many cases, cure. In contrast to patients with other haematological diseases requiring chemotherapy, the treatment of the majority of patients with CML requires life-long daily medication, and so the approach to management is rather different. Chemotherapy protocols for the acute leukaemias and lymphoproliferative disorders are chosen with consideration of the maintenance of gonadal function and few of the modern first-line therapies induce permanent gonadal failure. Parenthood in survivors of haematological cancers is therefore not a rare event. There does not appear to be an increased risk to the fetus from the mother's prior exposure to drugs. Neither is there any suggestion that recurrence of disease is more likely during or shortly after pregnancy [1]. However conception is unusual in both male and female survivors of transplantation and also in individuals who have received many lines of chemotherapy for episodes of disease relapse [2]. Modern haematologists have become increasingly aware of the need to preserve fertility from the time of diagnosis as it is often difficult to predict which patients may require further intensive therapy with or without transplantation. A significant minority of patients with CML will fail treatment with TKI and be considered for transplantation as second or third line therapy [3], so the issue of fertility preservation must continue to be addressed at diagnosis in all patients of child-bearing age.

Using the tyrosine kinase inhibitors before, during and after pregnancy

Imatinib was introduced into routine frontline treatment in 2001 and as a continuous single daily oral therapy, offers durable remissions for 65–70% of patients [3,4]. The duration of chronic phase is now expected to be in excess of 12–15 years. Because of this excellent disease control and remarkably few side effects, patients now enjoy near normal lifestyles. With this has come a renewed interest in parenting children but few data are available on either the effect of the TKI on gonadal function and subsequent fertility or on the risks to the fetus by continuing treatment during the pregnancy. In this context it is important to remember that Bcr-Abl is not the only target of the TKI: imatinib inhibits not only Abl but also c-kit, the platelet derived growth factor receptors alpha and beta (PDGFRA/B), arg and c-fms. Dasatinib, one of the second generation TKI, also inhibits Src and related proteins. A number of these proteins are known to have functions that might be important in gonadal development, implantation and fetal development [5–12].

TKI effects on fertility

Evidence from animal studies

Males. Animal studies investigating the effects of imatinib on gonadal function have yielded confusing results. During the development of the drug, male rats were given imatinib 60 mg/kg for seventy days (a dose deemed equivalent to the human dose of 600 mg/day) (http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf). Imatinib exposure resulted in lower epididymal and testicular weight along with reduction in the number of motile sperm. This was not seen at doses ≤ 20 mg/kg (equivalent to 200 mg/day). The fertility of male and female rats was not affected. Similarly, when immature male rats (aged 5–7 days) were exposed to a similar dose of imatinib for only three days, Nurmio et al observed interference with several maturation processes in the rat testis, including gonocyte migration, growth of the testis, formation of spermatogonial stem cell and Leydig cell pools and the proliferation of differentiating type A spermatogonia. Surprisingly however, by at the age of 11 weeks the exposed animals had normal epididymal sperm counts although the gonadotrophins, follicle stimulating hormone (FSH) and luteinising hormone (LH) remained elevated above normal levels. The authors concluded that treatment with imatinib early in life caused a permanent reduction in testicular size and resulted into altered reproductive hormone levels suggesting the action of compensatory mechanisms designed to maintain normal testicular function. They speculated that treatment with imatinib before puberty may have more deleterious effects than exposure in adult men [10]. Their data have subsequently been confirmed by Basciani et al who administered intra-peritoneal imatinib (50 mg/kg) to newborn male mice for 5 days and observed a profound reduction of spermatogonia that recovered with age. These authors ascribed the effects of imatinib to inhibition of PDGFR- β which is known to be required for proliferation and migration of gonocytes in the early postnatal period [11]. Later adult male rats that had been treated with imatinib in early postnatal life demonstrated a reduction in litter size compared to untreated littermates. Reassuringly there were no differences in the fertility index, the live birth index, the sex ratio or the frequency of survival to the time of weaning [12].

In contrast groups of adult mice of both genders were exposed to imatinib at 150 mg/day continuously for two months. Spermatogenesis was studied by the microscopy of the seminiferous tubules together with measurement of their diameter (an index of spermatogenic activity) and determination of the number of sperm. Again there were no differences seen between treated and untreated mice (Melo and Gosden, personal communication). This would suggest that intermediate term treatment, at least in adult mice, is not associated with impairment of gonadal function.

During drug development adult male rats were exposed to nilotinib at doses up to 180 mg/kg/day. A significant decrease in total epididymal weight was observed at a dose level of 180 mg/kg/day. All other male reproductive parameters including sperm counts and sperm motility were unaffected by treatment. It was thought unlikely that nilotinib will adversely affect male fertility (Novartis: nilotinib investigator's brochure). Dasatinib does not appear to affect fertility in male rats at doses < 10 mg/kg/day and was not toxic to the offspring at these doses (Bristol Myers Squibb: dasatinib investigator's brochure).

Females. Data relating to the effects of the tyrosine kinase inhibitors on ovarian function are sparse. During the development of imatinib for clinical use female rats were given imatinib 14 days prior to mating and through to Day 6 of gestation. Fertility was not affected. Rats given doses ≥ 45 mg/kg experienced post-implantation loss as evidenced by early fetal resorption or stillbirths, nonviable pups and early pup mortality between postpartum Days 0 and 4. If imatinib was administered during organogenesis at doses ≥ 100 mg/kg it induced teratogenic effects including exencephaly or encephalocele, absent or reduced frontal bones and absent parietal bones. At doses higher than 100 mg/kg, total fetal loss was noted in all animals. Fetal loss was not seen at doses ≤ 30 mg/kg (approximately equivalent to a 300 mg daily dose). In the first generation offspring at this same dose level, mean body weights were reduced from birth until terminal sacrifice. First generation offspring fertility was not affected. (http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf). In the studies of Melo

and Gosden, female mice were also given imatinib 150 mg/kg orally for two months. The ovaries were examined for morphological differences and for changes in the numbers of follicles at all stages of development (primordial, primary, secondary and tertiary). There were no differences observed between imatinib treated and control mice and in addition there was no increase in follicular atresia in the animals exposed to the TKI, suggesting that there may be no effect on fertility.

Female adult rats were given doses of nilotinib >60 mg/kg/day and no effects were observed on estrous cycles, pregnancy, or mating data. Based on these data the manufacturers do not expect that nilotinib will induce female infertility (Novartis: nilotinib investigator's brochure). Dastinib did not affect mating or fertility in rats at doses up to 10 mg/kg/day. However it was embryolethal in rats at all dosages and in rabbits if given early in gestation. When given at later stages in gestation, fetal skeletal abnormalities were observed in both species (Bristol Myers Squibb: dasatinib investigator's brochure).

Effects on fertility in humans

A recent publication has described the development of oligospermia after exposure to imatinib [13] and another reported the occurrence of primary ovarian failure in a 30 year old woman within two years of starting imatinib [14]. Although these reports have not been substantiated it would seem prudent to continue to recommend strategies to preserve fertility from the time of diagnosis. Adult male patients should be offered semen cryopreservation and is unfortunate that we are still unable to provide a realistic hope of future parenting ability to boys diagnosed prior to the onset of puberty. Female patients of child-bearing age with stable partners may wish to consider embryo cryopreservation. Those without partners should be referred for discussion of ovarian and/or oocyte retrieval and storage.

TKI effects during conception and pregnancy

Males

There is increasing evidence that children born to men who were taking imatinib at the time of conception do not have an increased risk of congenital malformations. An early report from the Novartis group described thirteen pregnancies in the partners of men who were taking imatinib at the time of conception. The outcome was known for only eight of these; three ended in abortion (two therapeutic and one spontaneous), there was one death in utero at 13 weeks and four normal pregnancies resulting in 4 normal infants [15]. A later report from MD Anderson was more encouraging with seven normal pregnancies and one spontaneous abortion in the partners of eight men treated with imatinib for a median of 20 months. One of the infants was born with a malrotation of the gastrointestinal tract which required surgical correction [16]. Following these initial publications a further ten uneventful pregnancies were reported in the partners of nine men on both standard and high doses of imatinib [17,18]. More recently Novartis have indicated awareness of more than sixty pregnancies in the partners of imatinib-treated men without any suggestion of an increased risk of pregnancy associated complications or congenital abnormalities (personal communication).

Very limited data are available for the outcome of children conceived while their fathers were taking dasatinib. Of nine such cases the outcome has been reported for seven; all the children were healthy at birth [19].

Females

The literature contains a number of case reports of pregnancy outcome for women who either conceived whilst taking imatinib but ceased treatment either in the first trimester or who remained on drug throughout the pregnancy, and most reported favourable outcomes [20–35]. Most recently full outcome data have been reported for 125 women from a total of 180 known to have conceived whilst on imatinib and the results have given considerable concern regarding drug safety (Table 1) [36]. The majority of these women (70%) were exposed to imatinib only during the first trimester but 26% remained on treatment throughout their pregnancy, i.e. until elective or spontaneous abortion or birth.

Table 1
outcome of pregnancies associated with the use of imatinib.

Pregnancy outcome	Number
Elective abortion (fetal abnormalities identified)	3
Elective abortion (fetal abnormalities unknown)	32
Spontaneous abortion	18
Still birth with fetal abnormalities	1
Live births with fetal abnormalities	8
Normal live births	63
Outcome unknown	55
Total	180

Sixty-three of the 125 pregnancies with a known outcome resulted in the birth of normal live infants. Eighteen of these women received imatinib for the duration of their pregnancy. Thirty-five women (28%) underwent elective terminations, 3 following the identification of fetal abnormalities. The remaining fetuses were either not examined or had no defects identified. 18 pregnancies (14.4%) ended in spontaneous abortion which is within the limits expected in the normal population (10%–15%). Of the remaining 9 infants, there were 8 live-births and one still birth, all with congenital abnormalities.

In total 12 pregnancies resulted in infants with fetal abnormalities. The dose (but not the exact duration) of imatinib taken by the mother was known for 10 of these cases but the data were insufficient to assess any potential relationship between cumulative dosage and the occurrence of fetal abnormalities. There were no reports of maternal exposure to alcohol, tobacco or drug addiction during pregnancy in any of these cases and none of the mothers had received any high dose chemotherapy prior to their pregnancies. Table 2 provides additional details of the defects seen in the 9 infants born with abnormalities (3 women underwent elective abortion because of identified abnormalities). Cases 2–4 are of note as the combinations of defects were strikingly similar and because similar bony defects were observed in the rodent studies. The expected incidence of exomphalos in the general population is approximately 1 in 3–4,000 births [37] and the finding of 3 cases out of 180 is far higher than would be predicted. The most likely candidate whose inhibition might be responsible for the induction of these abnormalities is the tyrosine kinase receptor PDGFR α . Mice homozygous for null mutations in PDGFR α demonstrated birth defects including facial clefting, severe spina bifida occulta, cardiac defects, omphalocele, renal and urogenital anomalies and vertebral and rib fusion abnormalities [6,38]. These data are derived from spontaneous reports and therefore subject to some potential reporting bias but remain the most comprehensive set of data on the effect of imatinib on pregnancy. The information is sufficiently concerning to advise all female patients to avoid conception whilst taking imatinib.

To date there is no information relating to the use of nilotinib before or during human pregnancy. During drug development nilotinib was administered to pregnant rats and rabbits. The fetal tissue concentrations were approximately 10% of those in the maternal serum, except for fetal rat liver, where

Table 2
congenital abnormalities described in children born to women who conceived whilst taking imatinib.

Infant	Abnormalities
1	Premature closure of the skull sutures (craniosynostosis)
2	Hypoplastic lungs, exomphalos , duplex left kidney, absent right kidney, hemivertebrae and a right shoulder anomaly
3	Exomphalos , right renal agenesis and hemivertebrae
4	Exomphalos and scoliosis
5	Communicating hydrocephalus, cerebellar hypoplasia, and cardiac defects
6	Meningocele (stillborn)
7	Hypospadias
8	Hypospadias
9	Pyloric stenosis

concentrations were 1.6 fold higher than in the parent. There was no evidence of teratogenicity in the rabbit or the rat but nilotinib was embryo- and fetotoxic in the rat and the rabbit at doses that induced maternal toxicity. Skeletal abnormalities including incomplete ossification of cervical vertebra were observed in both rat and rabbit fetuses. In rats administration of doses >30 mg/kg/day was associated with embryo death (Novartis: nilotinib investigator's brochure).

When a single oral dose of [¹⁴C] dasatinib was given to pregnant rats, a relatively low level of radioactivity was found in fetal as compared to maternal tissues. The concentrations of dasatinib-equivalents in fetal liver and kidneys were <13% of the respective maternal organs. The C_{max} of dasatinib-equivalents in fetal blood was approximately 39% of that in maternal blood. These data would predict a significant exposure to the fetuses of pregnant women receiving dasatinib [39]. Unsurprisingly data are sparse for the outcome of pregnancies associated with the use of dasatinib. The MD Anderson group reported a total of thirteen women who conceived children while on dasatinib. They had been taking dasatinib for a median of eight months (range 1–30 months) prior to conception. All ceased taking the drug on confirmation of their pregnancy and the outcome was known for eight women. Four elected for termination and two others experienced spontaneous abortions. One normal healthy infant had been born and one further child had been born 'small for dates' [19].

TKI effects post-partum

Imatinib and its metabolites are extensively excreted in the milk of female rats administered 100 mg/kg daily. The concentration in the milk was approximately three-fold higher than in plasma. Estimates suggested that approximately 1.5% of a maternal dose would be excreted into milk, which is equivalent to a dose to the infant of 30% the maternal dose per unit body weight. Subsequently imatinib levels have been measured in the milk of women taking imatinib post partum. Two of the three reports have identified substantial excretion of imatinib into breast milk and disturbingly in one patient, the active metabolite *N*-DesM-IM accumulated about threefold in breast milk as compared to plasma levels [40–42]. Because of the potential for serious adverse reactions in nursing infants from imatinib, breast feeding should be strongly discouraged.

Following an oral dose (20 mg/kg) of radioactive nilotinib to lactating rats, parent drug and its metabolites were found in the breast milk. Unchanged nilotinib was present at higher concentrations in rat milk compared to that observed in plasma. Extrapolating these data to humans, it is estimated that the maximum amount of nilotinib and/or its metabolites that a breast-fed infant could be exposed to by ingesting 1 L of milk daily is 0.26% of a 400 mg adult dose.

Following a single oral dose of radioactive dasatinib at 10 mg/kg to pregnant rats, the drug was readily found in breast milk. [¹⁴C]Dasatinib-derived radioactivity was detected at all time points through to the final measurement seventy-two hours later. The concentration of dasatinib-equivalents in milk at each time point was higher than that in maternal plasma or blood. The milk/plasma concentration ratios ranged from 2.4 to 37.2 strongly suggesting that active transporter(s) are involved in the lacteal secretion of dasatinib. The majority of the total radioactivity in milk was attributed to unchanged dasatinib.

Management of CML during pregnancy

There are two distinct scenarios involving pregnancy and CML. The first occurs when the pregnancy antedates the diagnosis such that this is made when the patient has the blood tests associated with planning the management of the pregnancy, usually in the early part of the second trimester. The second is when pregnancy occurs, planned or unplanned, after the diagnosis has been made and treatment has already been initiated. There are clearly important similarities between the two situations, particularly with respect to the subsequent management, as therapies other than the TKI may be necessary for disease control until delivery.

Diagnosis during an established pregnancy

The occurrence of CML in women of child-bearing age is a rare event but diagnosis in pregnancy is more common than might be expected. This is undoubtedly an opportunistic observation and is

explained by the blood counts performed in early pregnancy being the first such measurement in that individual's recent lifetime. Diagnosis at this time adds considerable complexity to management as for the patient, fear of the risk to the infant and loss of the happiness usually associated with pregnancy is added to the trauma of receiving the diagnosis of a potentially fatal disease.

For pregnant patients with CML in chronic phase, treatment is probably unnecessary if the white cell count remains below $100 \times 10^9/l$ and the platelet count is less than $500 \times 10^9/l$. Therapies other than TKI include interferon- α (IFN- α), hydroxycarbamide, busulphan and leucapheresis. If treatment is required in pregnancy hydroxycarbamide and busulphan should be avoided (Table 3). Busulphan is an alkylating agent that does not alter the natural course of the disease and is inferior to both hydroxyurea and IFN- α in terms of overall and progression free survival. It is now rarely used in the management of CML in chronic phase and should certainly be avoided in pregnancy [43,44]. There are case reports involving 5 women with a history of CML, treated with hydroxycarbamide at the time of conception, all of whom continued the drug during pregnancy. Four of these women delivered normal infants. The remaining woman developed eclampsia at 26 weeks gestation and a morphologically normal male infant was subsequently delivered stillborn [45–48]. Overall it appears that the risk of teratogenicity is not as high as would be suggested by the animal models, but again it is prudent to avoid this drug in pregnancy unless no alternative exists. Hydroxycarbamide is known to be excreted in breast milk and therefore should not be given to lactating women [49].

Regular leucapheresis may avoid drug therapy and be particularly useful during the first trimester of pregnancy [25,50–53]. Occasionally it may not be possible to adequately control the platelet count by leucapheresis alone and aspirin or low molecular weight heparin (LMWH) may be required. The safety profile of both these agents in pregnancy has been investigated at some length with reassuring results [54–59]. For women requiring additional treatment during pregnancy, either due to intolerance of leucapheresis or poorly controlled counts, IFN- α may have a role in the 2nd and 3rd trimesters. There are numerous case reports of successful pregnancies in women receiving IFN- α at all stages of pregnancy and for a variety of conditions including CML [60–63]. Due to its large size (19,300 daltons) it would seem unlikely that IFN- α crosses the placental barrier to any great extent [64]. Thus the drug is probably safe in pregnancy although it would seem prudent to avoid its use if not essential. There are no data on the safety of interferon during breast-feeding and it is not known whether any components of the drug are excreted in breast milk.

Pregnancy after diagnosis and initiation of treatment

Unplanned pregnancies on imatinib. In the case of an unplanned pregnancy whilst taking imatinib, balancing the risk to the fetus of continuing imatinib versus the risk to the mother of interrupting treatment remains difficult. From the fetal perspective imatinib should be discontinued due to the potential risk of serious developmental abnormalities but from the maternal perspective this may not be appropriate. Another option would be to continue imatinib and have the pregnancy closely monitored, considering termination should any significant abnormalities be identified. In these circumstances the couple should be made aware of potential risks particularly of 1st trimester exposure. Considerations include the wishes of the parents, the mother's disease status, the current response to imatinib, the availability of suitable alternative therapies and the ability to reinstate responses to imatinib after a prolonged period off treatment.

Table 3
reported effects on fertility and embryonic development of chemotherapy commonly used in chronic myeloid leukaemia.

Drug	Reported effects	Reference
Busulphan	Teratogenic in animal models, has been associated with birth defects in humans	[43,44]
Hydroxycarbamide	Fetal growth retardation, fetal death and an increased incidence of congenital anomalies including craniofacial, limb and trunk defects	[45–49]
Interferon- α	Non-teratogenic in rats and rabbits, resulting in normal offspring but has abortifacient effects in rhesus monkeys at doses of 90 and 180 times the recommended dose of 2 million iu/m ² .	[61–65]

Planned pregnancies on imatinib. The advice given to women who wish to become pregnant after the diagnosis and initial treatment of their disease will most probably differ according to the current response to treatment. Given the association of congenital abnormalities with first trimester exposure to imatinib, the drug should be discontinued before attempting to conceive. There is controversy concerning the time that should elapse between cessation of treatment and unprotected intercourse but it would seem reasonable to advise a few days to permit the wash-out of imatinib from the body.

For patients with optimal responses, i.e. in major or complete molecular remissions, patients can reasonably discontinue treatment to allow attempts at conception. Given that the patient will not take imatinib for the duration of the pregnancy it may be advisable to suggest that the period from stopping imatinib to becoming pregnant should not exceed 6 months. Patients such as these who have experienced very large reductions in tumour load are unlikely to require any therapy until after delivery, although regular monitoring by RT-PCR should be instigated. If the response to TKI is less good, then cessation may lead to cytogenetic and/or haematological relapse [65]. A plan for managing these pregnancies is presented in Table 4.

Ault et al previously reported 10 women who interrupted treatment with imatinib due to pregnancy [16]. Of the 9 in complete haematological response (CHR) when the imatinib was stopped, 6 had an increase in Ph-positive metaphases and five lost their CHR whilst off treatment. At a median of 18 months since restarting imatinib these 9 women were again in CHR and although all had a cytogenetic response this was complete in only 3. This might be considered a poor response as the rate of CCyR at 18 months in patients who received uninterrupted imatinib from diagnosis is 75%–90%. However as a group these 9 women showed improved responses to treatment following pregnancy when compared with their results pre-pregnancy. Reassurance that imatinib can be discontinued in some patients under certain favourable circumstances is provided by a recent report by Rousselot et al [66]. Imatinib was discontinued in 12 patients who had all been in complete molecular remission for a period of at least 2 years. Six developed molecular relapse within 5 months of stopping imatinib therapy but the remaining 6 in complete molecular remission at a median follow-up of 18 months. Of those who relapsed, the majority again achieved a complete molecular response within a relatively short period following reintroduction of imatinib.

Pregnancy in advanced phase disease. This is usually unplanned and is an extremely difficult management problem. The relevant data are largely derived from patients who develop acute leukaemia during pregnancy. In order to give the patient the best possible chance of achieving remission (or in the case of CML, a second chronic phase,) treatment should be administered promptly and subsequent courses should be delivered in a timely manner. Most patients with advanced phase disease will have previously been exposed to imatinib and prolonged responses to a second generation TKI are rarely durable. The alternative is the use of combination chemotherapy akin to that used in acute myeloblastic or lymphoblastic leukaemia. If the pregnancy is in the first trimester at the time of diagnosis, delaying treatment until after delivery is not an option as it is unlikely that either the

Table 4
optimising management of female patients with CML who are planning a pregnancy.

Pre-conception	Ideally 24 months in MMoIR before discontinuing imatinib Counselling re risk to infant if imatinib is continued and risk to mother is imatinib is discontinued Time-limit attempts at conception to prevent very prolonged periods off treatment
Imatinib wash-out	Unknown but no more than 7 days
Disease monitoring	Blood counts monthly, RQ-PCR 2–3 monthly No treatment if CMoIR/MMoIR Consider treatment if loss of MMoIR or CCyR Give treatment if loss of CHR Leucapheresis in 1st trimester if treatment required Leucapheresis and/or IFN- α in 2nd and/or 3rd trimester if treatment required
Post-delivery	Re-start imatinib with urgency dependent on RT-PCR results. If MMoIR could permit breast feeding. For all other disease status, re-start imatinib and advise against breast feeding

mother or the child would survive until term. Chemotherapy given during the 1st trimester for any malignancy carries the highest risk of congenital malformation, estimated from studies in acute leukaemia to be between 10–23%. The possible impact of intensive chemotherapy upon fetal development during the first trimester of pregnancy must be explained. It is also important that the mother realises the consequences to her own health of delaying such treatment. In this situation most women will elect for termination.

Administration of combination chemotherapy during the 2nd and 3rd trimesters is widely accepted as being associated with fewer complications and in general the later in pregnancy the chemotherapy is given, the fewer the risks to the foetus. However caution should be exercised when administering chemotherapy near the time of delivery. Ideally patients should have recovered from the therapy induced pancytopenia prior to delivery. If the leukaemia presents late in pregnancy there is a strong case for early delivery with intensive supportive therapy with blood products and growth factors and a delay in the administration of chemotherapy. If treatment is deemed essential the attending obstetrician should be aware that the child may be born anaemic, neutropenic and/or thrombocytopenic. Appropriate measures must be taken at the time of delivery and it is important that the infant is closely monitored at this time and is followed up after birth. The use of the second generation TKI has not been described in this situation.

Summary

The tyrosine kinase inhibitors have over the space of a single decade, revolutionised the management of CML and radically changed the outlook for patients. CML has become a life-long chronic ailment, the management of which must now adapt to, rather than dictate, the patient's lifestyle. For male patients, fathering children can be achieved without interruption of treatment. For female patients and particularly those with more advanced disease, the management is rather more complicated. However with counselling and a considered approach to disease monitoring, most women wishing to conceive can be advised appropriately so as to minimise risk to both mother and infant.

CML in childhood

Introduction

Chronic myeloid leukaemia (CML) is rare in childhood, accounting for less than 10% of all cases of CML and less than 2% of all paediatric leukaemias [67]. The incidence is higher in adolescents (age 15–19 years) at 1.2 per million per year than in the younger children (0–14 years- 0.6–0.8 per million per year [68]. A Japanese registry study identified CML as the specific disease in 0.2% of all leukaemias in the age group 1–4 years, 2.2% for those aged 5–9 years, 3.7% at 10–14 years and 8.3% at 15–19 years) [69]. The disease is exceptionally rare in infancy.

There is no clear evidence of a hereditary predisposition as identical twins appear to be discordant for the disease and CML is no more common in the siblings of affected children. There is also no increased risk of CML in pre-leukemic chromosomal disorders such as Fanconi anemia and Down's syndrome. In occasional cases, an association with ionizing radiation has been described; a 7-fold increase in CML, particularly in children under 5 years of age, was reported in Japan following the nuclear explosions in the 1940s [70].

As a consequence of its rarity there are few studies of the disease and/or its management specifically in children and those that exist usually describe relatively small numbers of patients. In addition some of the older literature pertaining to CML may have included patients with juvenile myelomonocytic leukaemia. However the available literature suggests that the natural course of the disease and the response to treatment are similar to that seen in adults. The most pressing issue at the present time is the relative roles of TKI therapy and allogeneic stem cell transplantation (allo-SCT), given that there are no data regarding the very long-term use and therefore the safety, of the first and second generation TKI and that the outcome of allo-SCT is best in the youngest patients.

Presentation of CML in childhood

Millot and colleagues described the presenting features of forty children and adolescents treated at sixteen French centres [71]. Thirty-eight were diagnosed in chronic phase at a median age of 12.5 years (range 1–18 years). The diagnosis was made by chance in nine cases but in those who were symptomatic the median duration of symptoms was short at one month (range 0–5.5 months). The symptoms and signs were identical to those seen in adults with CML with 45% complaining of asthenia, 20% of splenic discomfort and 17.5% (7 patients) of weight loss and bleeding. Splenomegaly was present in 28 children (70%) and was more common in patients with higher white cell counts. In contrast the platelet count tended to be lower in those with splenomegaly. The median white cell count was $242 \times 10^9/l$ (range $10\text{--}720 \times 10^9/l$) which is rather higher than has been described in adults. Anaemia was present in 65% of the children and 60% had thrombocytosis.

Molecular biology

A number of authors have addressed the molecular basis of CML in children [71–75] with conflicting results. In adults there is general agreement that the b3a2 transcript is more common than b2a2 with 10–20% of patients expressing both transcripts. The pattern may be reversed in children although the clinical significance of this is unclear since early reports suggesting improved outcomes for patients expressing the b2a2 have not been substantiated [76]. A number of studies in adults have found an association between the expression of b3a2 and higher platelet counts at diagnosis [77–80]. Most recently Adler et al studied 146 children presenting with CML from 1995–2005 and treated within the GPOH CML-paed-1 protocol and confirmed a substantially higher platelet count at presentation in children expressing b3a2 than in children with b2a2 transcripts [75]. In addition they identified significantly higher white cell counts and haemoglobin levels associated with b3a2. Bone marrow blast counts tended to be lower in children co-expressing both transcripts. The most striking difference in this study was the surprising finding that males were more likely to express b2a2 than females and consequently females more likely to express b3a2 whilst co-expression of the transcripts was equally distributed in boys and girls. The only publication addressing this point in 226 adults [81] found the opposite with males more likely to express b3a2 (44% male, 34% female).

Treatment of CML in childhood and adolescence

Interferon

Prior to the introduction of the tyrosine kinase inhibitors into clinical practice the preferred management was that of stem cell transplantation. For those children without a donor or unsuitable for transplant, the primary therapy was interferon- α (IFN). Giona et al described the intermediate-term outcome of 30 patients diagnosed with CML in childhood and adolescence between 1980 and 2001. The eight year overall survival of 17 children who were given IFN was 63% compared to 61% of the 13 who received allo-SCT but all the IFN recipients had residual disease [82].

Data as to the efficacy of interferon in children are understandably limited. There have been seven large randomized trials in CML involving >2000 patients, some of which have included children [83] and several small paediatric studies [84,85]. Overall there seems to be no significant difference between the response of children to IFN- α compared to the response of young adults. In adults the overall response rate is 70%, with around 20% of patients achieving a major or complete cytogenetic response usually within six months [83]. The standard starting dose is 3 mega units (MU) daily by subcutaneous injection. The dose should be adjusted after the first few weeks of treatment to maintain the white cell count between 2 and $4 \times 10^9/l$ and platelets $>80 \times 10^9/l$ (maximum dose 5 MU daily).

Fourteen children were entered into a single arm study of interferon plus cytosine arabinoside in France [85]. By thirteen months, thirteen children had discontinued treatment for either imatinib or allo-SCT. Complete haematological remission (CHR) was achieved in seven of twelve evaluable children (58%) by three months, major cytogenetic remission (MCyR) in seven of eleven (50%) and complete cytogenetic remission (CCyR) in two of the seven (14%) by twelve months. Eight children experienced grade 3–4 toxicity. The rates of CHR, MCyR and CCyR are consistent with those observed in adults but

there was a higher rate of treatment interruptions (perhaps attributable to the addition of cytosine arabinoside) and treatment failure.

Allogeneic stem cell transplantation

The outcome of allo-SCT in children is similar to that of adults with registry studies suggesting an long-term overall survival of 60–75% [86,87]. The parameters that affect survival, i.e. the EBMT or Gratwohl score, apply equally well to children as to adults [88]. An early study from Germany described the outcome of 75 children newly diagnosed with CML of whom 47 were transplanted (27 from sibling, 16 from matched unrelated and 4 from family mismatched donors). The twelve year overall survival was 62% for transplanted patients versus 10% for those treated with chemotherapy [89]. These data supported our earlier approach of recommending allo-SCT for all children for whom a matched donor could be found.

A few years later Cwynarski et al analysed the outcome of 315 patients (some of whom would have been included in the previous study) reported to the registry of the European Group for Blood and Marrow Transplantation (EBMT). The overall survival at 3 years for children transplanted from sibling donors in first chronic phase was 75% compared to 46% if the transplant unrelated or mismatched was performed in more advanced phases [87]. The overall survivals for children transplanted from unrelated donors were not significantly different at 65% and 39% for chronic phase and advanced phase disease respectively. However the transplant related mortality (TRM) was higher for recipients of unrelated donor cells at 31% for chronic and 46% for advanced phases compared to 20% and 16% for recipients of related products. As expected the increased risk of TRM in recipient of unrelated transplants was offset by a reduced relapse rate and this was particularly marked in patients transplanted beyond chronic phase in whom the relapse rate was 20% compared to 49% for children receiving cells from sibling donor.

Relapse after transplant for CML is not uncommon in either chronic or advanced phases. However whereas those transplanted in, and relapsing in, chronic phase are highly likely to return to cytogenetic and molecular remission using either imatinib or donor lymphocyte infusions (DLI) the same is not true of advanced phase disease where responses to imatinib are generally short-lived and responses to DLI unusual. The 3 year disease free survivals of 35% and 34% for children receiving sibling and unrelated stem cells for advanced phase disease is encouraging and would place allo-SCT as the treatment of choice for patients who have progressed beyond 1st chronic phase.

The outcome of seventy-six children transplanted for CML in France was reported in 2003 and it is likely that there was considerable overlap with patients in the EBMT registry study. The overall and progression free survivals of children transplanted in 1st chronic phase were 73% and 73% respectively and 27% and 27% for those who received transplants for advanced phase disease. Procedural related mortality accounted for more than 90% of the deaths and the single most frequent cause of death was graft versus host disease (GvHD) [90].

There has been one attempt at a prospective study of transplant, using the availability of a donor as a genetic randomisation. CML-Paed-1 (1995–2004) aimed to transplant children with sibling donors within 6 months and those with unrelated donors within 12 months of diagnosis, after cytoreductive treatment with hydroxycarbamide. The overall survival at 5 years for recipients of sibling donors was 87% but disappointingly only 52% from an unrelated donor (matched) and 47% from a mismatched unrelated donor. The trial was stopped in 2004 because of lack of recruitment.

Data relating to the role of reduced intensity conditioning (RIC) in children is sparse and as yet uninformative [91,92]. An EBMT study of RIC transplantation in patients of all ages with CML reported to the EBMT registry contained very few patients under the age of twenty years. Although the group was heterogeneous with respect to disease phase, duration, conditioning regimen and stem cell source, the three year overall survival for patients with low Gratwohl/EBMT scores (0–2) was similar in both RIC and myeloablative groups [93]. Since RIC transplants are associated with a considerable risk of disease recurrence such that long-term disease free survival is less likely after RIC transplants than after standard conditioning, there seems little to be gained from using the less intensive approach in this population of patients. Similarly it is unlikely that RIC transplants will cure advanced phase disease and so numbers of young patients suitable for these procedures will be limited.

Consideration of RIC transplants in CML reminds us that these procedures achieve their effect largely through an allo-immune response and that CML is the disease in which these approaches should be most successful. Monitoring for minimal residual disease (MRD) is therefore mandatory after any form of transplant for CML [94]. The choice of therapy for disease recurrence is also controversial with both DLI and TKI having the potential to achieve molecular remissions [95,96]. DLI remain the most effective means of restoring durable remissions but are associated with an increased risk of acute and chronic GvHD. Children who require DLI should be managed, as adults, with escalating doses of DLI over many months and as indicated by the results of molecular monitoring. Levine et al reported 49 children who received DLI for disease recurrence between 1991 and 1999 [97]. Some patients were treated prior to the introduction of the escalating dose approach and only eight were transplanted for CML, so the value of these results is somewhat limited today. However some themes common to adult practice emerged: DLI were unlikely to be successful if the relapse occurred within six months of transplant and improved survivals were associated with the occurrence of grade 1–2 GvHD.

There may be a few individuals who experience relapse after allo-SCT and have never been treated with imatinib, and for these a trial of imatinib would be an entirely reasonable alternative. Certainly imatinib rather than DLI should be used if the relapse occurs within one year of transplant and/or if the child has active GvHD, so as to avoid severe GvHD. However the numbers of such patients is diminishing and those experiencing relapse post transplant are likely to have been transplanted because of imatinib failure. The use of a TKI here, even a second generation drug, is less rational. In adult patients who have received a 2G-TKI for imatinib failure, complete cytogenetic responses are more predictable in those who tolerated imatinib without cytopenias, who had a low Sokal score at diagnosis and who had cytogenetic responses to imatinib [98]. It is possible that a child who relapses post transplant for imatinib failure and who satisfies these criteria may benefit long-term from a 2G-TKI and this should be considered ahead of DLI.

Imatinib

The outstanding efficacy of imatinib in CML is not associated with age and children respond as well as adults to TKI. As for all other forms of treatment data specific to children is scarce. The efficacy and side effects of first-line imatinib therapy have now been evaluated in Phase I and II trials with a total of less than 100 children. Champagne et al described the efficacy of imatinib in 31 children of median age fourteen years (range 3–20 years) who received imatinib after IFN-failure [99]. Fourteen children were in chronic phase at the time of imatinib therapy: CHR occurred in all and ten of twelve (83%) evaluable children achieved CCyR. This response was later lost in two patients. Responses were seen in more advanced phases but were not durable. Pharmacokinetics suggested that a once daily dose of 260–340 mg/m² was equivalent to 400 mg daily for adults. The recommended starting doses are 260 mg/m² for children in chronic phase but previously treated with interferon and/or allo-SCT, 340 mg/m² for those with newly diagnosed chronic phase disease (with a maximum dose of 600 mg daily), 400 mg/m² (with a maximum dose of 500 mg/m²) for accelerated phase and 500 mg/m² (maximum 800 mg/m²) for blast crisis. Children, like adults, exhibited marked interpatient variability in plasma concentration. Clearance of imatinib was identical to that seen in older patients. The observed adverse events were also similar to those seen in adults.

Imatinib was licensed for use in children in 2003 and interestingly the FDA approved this use on the proviso that manufacturer agreed to do trials in this patient population. The side effects of nausea, vomiting, diarrhoea, rash, fluid retention, cytopenias and hepatotoxicity occur with the same frequency and severity as in adults. There is no known incidence of cardiac failure but this might be a worrying issue for long term therapy. Imatinib impairs osteoblast and osteoclast differentiation and activity and is well known to cause hypocalcaemia and hypophosphatemia. These effects might have potential long term effects on growth and development [100–102].

Second generation tyrosine kinase inhibitors

To date there are no data available for the use of nilotinib in young patients. There is an urgent need for well designed clinical trials in this patient population. Two studies of the use of dasatinib in children and adolescents have been presented at international meetings. Aplenc et al described preliminary

Table 5

arguments for and against allogeneic stem cell transplantation (allo-SCT) as first-line therapy for CML in children and adolescents.

For Allo-SCT	Against Allo-SCT
Targeted therapy commenced in childhood will potentially be administered for decades: the long-term effects are unknown	Allo-SCT is associated with considerable procedural related mortality and in survivors, potentially severe long-term morbidity
Allo-SCT is best performed in chronic phase within 12 months of diagnosis	Imatinib given pre-transplant does not adversely affect the outcome of transplant and the effect of time to transplant on overall survival may no longer be important
Delay to transplant increases the risk of development of disease progression: transplant in advanced phase disease is largely unsuccessful	Disease response and loss of response can now be carefully monitored using RT-PCR such that transplant can be performed before disease progression

data in 35 children of median age 11 years (range 2–20 years) who received dasatinib in a Phase I dose escalating study in both solid tumours and Ph⁺ leukaemias. Doses up to 85 mg/m²/bd were well tolerated initially. Diarrhoea and headache were dose limiting toxicities at the higher dose of 110 mg/m²/bd but pleural effusions and gastrointestinal haemorrhage were observed with prolonged use at the lower doses. Of the six children with CML, five had obtained useful responses [103]. The Bristol Myers Squibb sponsored Phase I/II study CA180018 of dasatinib in children and adolescents with relapsed or refractory leukaemia has entered 16 children with CML (8 in Cp and 8 in more advanced phases). The response in chronic phase was excellent with 4 of 6 children on 60 mg/m²/day and both children on 80 mg/m²/day achieving CCyR. Only 3 episodes of Grade 3/4 toxicities had been observed at the time of reporting comprising headache, nausea and vomiting [104]. Pharmacokinetics from both studies suggest that the half-life of dasatinib in patients under the age of 20 years may be somewhat shorter at approximately 2 hours than that seen in adults at over 3 hours.

Allogeneic stem cell transplantation or a TKI?

In adult practice imatinib (or entry into a study involving a 2G-TKI) is considered to be the optimal first line therapy. Here the controversy lies between allo-SCT and a 2G-TKI as second line management. In children however there may still be worthwhile debate about the initial treatment (Table 5). The argument for TKI includes the fact that some 65–70% of patients who achieve a CCyR seem to have an excellent prognosis [4,105] and with time, increasing numbers of these patients achieve MMR. Those individuals who fail to respond to imatinib can be identified by the lack or loss of a response and can be rapidly moved to allo-SCT or a 2G-TKI. Furthermore the long-term sequelae of allo-SCT in children, including chronic GvHD (cGvHD), infertility and endocrine deficiencies are not inconsequential. For instance the final height of patients transplanted as children is lower than would be predicted using the parents' heights. The poorest growth rates are seen in children under the age of ten years at transplant and in those who received radiation to the central nervous system [106]. A number of studies have described the long-term complications of transplantation. Of 316 surviving

Table 6a

developing a risk score for factors influencing the probability of complete cytogenetic responses to second line tyrosine kinase inhibitors.

Factor	Score
Best cytogenetic response on imatinib	100% Ph-negative
	5–99% Ph negative
	< 5% Ph negative
Sokal risk score	Low
	Intermediate/high
Neutropenia requiring G-CSF support while on imatinib	No
	Yes
Time from imatinib failure to second generation TKI	0.001 points per day

Table 6b
predicting the response to second generation TKI by risk score.

Risk Group	Score	Probability of CCyR at 12 months
Good	<1.5	100%
Intermediate	1-5-2.5	58%
Poor	> 2,5	21%

patients who received myeloablative transplants for CML, more than 90% reported normal or minimal impairment of health with 72-88% having returned to school or work [107]. However 47% had developed cataracts, 10% experienced avascular necrosis (particularly associated with the use of total body irradiation and/or the occurrence of cGVHD) and 15% developed pulmonary disease. The BMT Survivor Study group have reported specifically on the late effects of transplant for CML across all age groups. They described relative risks of developing cataracts, avascular necrosis, osteoporosis, exercise induced dyspnoea, endocrine impairment and hepatitis of 15.3, 12.0, 6.4, 4.2, 3.2 and 2.9 respectively, in patients compared to their healthy siblings. Of the control group 94% rated their health as good, very good or excellent compared to only 78% of the transplant recipients [108]. The same study group have also investigated the long-term outcome of children treated by allo-SCT for a variety of diseases. Compared to a control group of siblings of survivors of childhood cancer, recipients of allo-SCT who had survived more than two years post-graft were more likely to have received special education, to report physical limitations and to have behaviours that impaired social competence [109]. In addition increased risks were found for motor and sensory impairment, hearing and visual loss and persistent pain [110].

Arguments against TKI and for allo-SCT in children comprise the acknowledgement that the majority of imatinib responders will require life-long treatment and the long-term side effects of the TKI are completely unknown, delay of transplant beyond one year from diagnosis adversely affects transplant outcome, awareness that imatinib failure (as defined by progression to advanced phase disease) appears to occur early in the disease course [4] and subjecting these patients to a trial of imatinib prior to allo-SCT may result in transplant beyond first chronic phase and thereby jeopardise their chance of long-term survival. In general however the consensus is that all patients newly diagnosed with CML and irrespective of their age should be given a trial of a TKI. Early concerns that the use of imatinib prior to transplant might jeopardise overall survival seem to be unsubstantiated [111–114]. The younger the patient the more attention should be paid to achievement of imatinib responses as defined by the ELN [115] and rapid referral for a change in management, including consideration of allo-SCT, should these milestones not be reached. With this approach it is advisable to conduct a donor search soon after diagnosis. There might be an additional argument in young patients for requiring the achievement of a major molecular response after 18 months treatment with imatinib (currently defined as a sub-optimal response) as loss of complete cytogenetic response to imatinib is more common in those who have not achieved the depth of response defined as MMR [116].

Management at the time of imatinib failure is also not straightforward. For patients who remain in chronic phase the obvious choices are a 2G-TKI or allo-SCT. Approximately 40% of patients with imatinib resistance will achieve CCyR on a 2G-TKI but the majority will not [117,118]. The durability of these responses beyond two years is as yet unknown. Milojkovic et al have identified some prognostic factors for response to a 2G-TKI and these may prove useful in decision making [98] (Table 6). Young patients with poor prognostic features could be referred directly for allo-SCT, particularly if they have suitable sibling or well matched unrelated volunteer donors. In those at good or intermediate risk, and/or those with less than optimal donors, a trial of a 2G-TKI would be reasonable. At least two groups have suggested that cytogenetic responses to the 2G-TKI can be predicted by the achievement of any cytogenetic response at three months and so this timepoint seems to be critical [98,119]. If there is evidence of disease progression and/or if imatinib resistance is associated with the emergence of the T315I kinase domain mutation, then the only therapy to offer any chance of long-term survival is allo-SCT. Use of a 2G-TKI in this situation is simply to attempt to restore a second chronic phase prior to transplant and allow time to identify a donor. Since the onset of disease progression

remains unpredictable this is further justification for identifying a donor as early as possible in the disease course.

Summary

CML in children and adolescents seems to be identical to the disease seen in adults in terms of presenting features and response to treatment. Despite the lack of information regarding the very long-term effects of the TKI, young patients with CML should receive imatinib as their first treatment. Because allo-SCT remains an excellent treatment for CML, we should require children to respond 'optimally' to imatinib. Serious consideration should be given to using allo-SCT as the second-line therapy for any patient responding sub-optimally to TKI. Every effort should be made to find a suitable donor for any younger patient experiencing disease progression.

Practice Points 1

Effects of TKI in fertility and pregnancy

- The body of evidence to date suggests that the tyrosine kinase inhibitors do not adversely affect fertility in men or women. However until we have more follow-up it is reasonable to continue to consider strategies to preserve fertility at diagnosis
- Children born to men who were taking imatinib at the time of conception appear to be healthy. Men planning to father children should no longer be advised to discontinue treatment prior to conception
- Of the children born to women who were taking imatinib at the time of conception there has been a cluster of congenital abnormalities affecting skeletal and gastrointestinal development.
- Women taking imatinib should therefore be advised to discontinue imatinib prior to attempting conception. The advisability of discontinuing treatment in order to become pregnant will depend on the clinical response to imatinib
- Blood counts and RT-PCR levels should be monitored regularly throughout the pregnancy
- There are virtually no data regarding the use of dasatinib or nilotinib in pregnancy. Women must be advised to discontinue these drugs if they wish to become pregnant.

Practice Points 2

Managing CML ante- and post-partum

- If possible chemotherapy should be avoided in women with CML who are diagnosed in pregnancy or who become pregnant during the course of their disease
- If the white cell count remains below $100 \times 10^9/l$ no therapeutic intervention is required
- If the platelet count is elevated above $500 \times 10^9/l$, aspirin and low molecular weight heparins can be used safely.
- In the first trimester the white cell and platelet counts can be controlled by leucapheresis
- Leucapheresis can be continued throughout the second and third trimesters and is usually required less often in the third trimester
- If chemotherapy is required in the second and third trimesters, interferon- α is the recommended therapy
- All chemotherapy should be avoided if the mother is breast feeding

Practice Points 3

Features of CML in Childhood

- CML is a rare disease in childhood accounting for less than 2% of all childhood leukaemias. It is extremely rare in infancy and there is no evidence of any hereditary predisposition
- The presenting features in children are identical to those in adults. Translocations involving b2a2 may be more common in boys than in girls. The clinical significance of this is unclear
- Imatinib is the first-line treatment in CML, irrespective of age
- The response to imatinib in children is identical to that in adults
- Children and adolescents responding sub-optimally to, or failing imatinib should be referred for allo-SCT in preference to a second generation TKI
- Any young patient experiencing disease progression should be offered allo-SCT as soon as possible, preferably after induction of a second chronic phase

Research Agenda 1

CML in Pregnancy and Childhood

- The current recommendation is that women planning to become pregnant should discontinue treatment. More information is required as to the effect of treatment cessation and on the reintroduction of therapy on the disease course.
- Additional work is required to identify the mechanism of congenital malformations occurring on imatinib. Data relating to the effects of the second generation tyrosine kinase inhibitors on fertility and fetal development are very limited.
- To date, information regarding the use of the second generation tyrosine kinase inhibitors in childhood is extremely limited. There is an urgent need for clinical trials of these targeted agents in children and adolescents

Conflict of interest

None.

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