



REVIEW

# How I treat acute and chronic leukemia in pregnancy

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## KEYWORDS

Leukemia;  
Pregnancy;  
Chemotherapy;  
Malformations;  
Fetus;  
Breast feeding

**Summary** The prevalence of pregnancy associated leukemia is approximately 1 case out of 10,000 pregnancies. This rare occurrence precludes the conducting of large, prospective studies to examine diagnostic, management and outcome issues. The treatment of a pregnant woman with leukemia may be associated with severe adverse fetal outcome including death and malformations, and therefore poses a difficult challenge for both the patient and the attending physician. Chemotherapy during the 1st trimester is associated with an increased risk for congenital malformations. However, this risk diminishes as pregnancy advances.

When acute leukemia is diagnosed during the 1st trimester, patients should be treated promptly similar to non-pregnant patients. However, the aggressive induction therapy should follow pregnancy termination. When the diagnosis is made later in pregnancy standard chemotherapy regimen should be considered and usually pregnancy termination is not mandatory. However, both the mother and the fetus should be under close observation and delivery should be postponed to a non-cytopenic period. Pregnancy associated chronic myelogenous leukemia (CML) can be treated with interferon throughout pregnancy with no apparent increase in adverse fetal outcome. In the very rare case of chronic lymphocytic leukemia (CLL) during pregnancy treatment can usually be delayed until after delivery.

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## Introduction

The diagnosis of leukemia during pregnancy is a dramatic event that poses challenges to the pregnant patient, her family and the medical team.

The fact that an optimal anti-leukemia treatment may be associated with adverse fetal outcome including severe malformations or death raises a complicated maternal-fetal conflict. The dilemma is relevant especially in cases of acute leukemia. The aggressiveness of the disease requires immediate administration of intensive multi-drug chemotherapy and is further complicated by the disparity between the quality of the limited avail-

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able clinical experience versus the dramatic decisions that has to be taken.

Due to its relative rarity, and the absence of a central registry, the epidemiology of leukemia occurring during pregnancy has never been well studied. Therefore, the prevalence of pregnancy associated leukemia is based on estimations and seems to be approximately 10,000 pregnancies.<sup>1-3</sup> This occurrence may become higher, following the current trend to postpone pregnancy until later in life and the increase in the incidence of acute myelogenous leukemia (AML) in the last decade.

It has been estimated that the majority of leukemias diagnosed during pregnancy are acute.<sup>1-4</sup> Of the acute leukemias, two thirds are myelogenous and one third is lymphocytic. Chronic myelogenous leukemia (CML) occurs in up to 10% of pregnancy associated leukemias<sup>5</sup> and chronic lymphocytic leukemia (CLL) is extremely rare.<sup>5,6</sup> The relative rarity of pregnancy-associated leukemia precludes conducting large prospective studies to examine diagnostic, management and outcome issues and the literature is largely composed of small retrospective studies and case reports. In this article we critically review the available data, identify clinical and ethical dilemmas and unresolved issues and suggest possible solutions regarding different aspects of leukemia diagnosed during pregnancy and lactation.

## Design and Methods

We systematically searched English literature using the MEDLINE database for the years 1977-2007, the UptoDate and the NIH websites. The search terms were combinations of "pregnancy" and / or "leukemia" with each of the medications and treatment measures mentioned in this review. The literature search resulted in 5,212 articles, but only relevant data regarding the diagnosis and treatment of leukemia during pregnancy were analyzed. Letters were included when relevant cases were reported in them. The relevant articles summed to about 500. All titles and abstracts were evaluated for the treatment options during the various trimesters of pregnancy and stages of disease. The references in these articles were also reviewed in order to establish additional relevant papers that could contribute to our review.

## Diagnosis of leukemia during pregnancy

During pregnancy the woman's body undergoes physiological changes that may make the diagnosis of leukemia more challenging. The diagnosis may

be delayed since non-specific symptoms and signs of leukemia such as weakness, fatigue, pallor and dyspnea are sometimes attributed to gestation. Furthermore, pregnancy itself may be associated with anemia and leukocytosis that are common laboratory findings in patients with leukemia. Nevertheless, there is no evidence suggesting a delay in the diagnosis of leukemia in pregnant patients compared to non-pregnant controls.

The diagnosis of leukemia requires a morphologic, immunophenotypic and cytogenetic examination of bone marrow samples. Similar to all other biopsies done under local anesthesia, a bone marrow biopsy can be safely performed during pregnancy without harming the fetus.<sup>7</sup>

## Treatment of leukemia during pregnancy- general principles

### Chemotherapy during pregnancy

Since the different cytotoxic agents have a molecular weight of 250-400 kDa, virtually all of them can cross the placenta and reach the fetus.<sup>8</sup> However, only a few small trans-placental studies have been conducted to assess drug concentrations in the amniotic fluid, cord blood, placental and fetal tissues - with conflicting results. When treating pregnant patients with chemotherapy, it is crucial to consider the normal physiological changes that occur during pregnancy including up to 50% increase in plasma volume and renal clearance of drugs, the third space created by the amniotic fluid and an accelerated hepatic oxidation.<sup>7,9</sup> These changes may decrease active drug concentrations compared with non-pregnant women. However, due to the absence of pharmacokinetic studies in pregnant women receiving chemotherapy, it is still unknown whether different doses of chemotherapy should be administered during pregnancy.

Almost all chemotherapeutic agents have been documented to be associated with congenital malformations in animal models.<sup>7,9</sup> However, the doses of chemotherapy used in humans are often lower than the minimum teratogenic doses applied in animals, making it difficult to extrapolate data from animals to humans.<sup>9</sup> Chemotherapy administered during the first trimester may increase the risk of spontaneous abortions, fetal death and major malformations.<sup>10,11</sup> Malformations reflect the gestational age at exposure and the most vulnerable period is during weeks 2-8 at which fetal organogenesis occurs.<sup>9</sup> During this period, damage to any developing organ may lead to fetal death or to major malformations. Several organs includ-

ing the eyes, genitalia, the hematopoietic system and the CNS remain vulnerable to chemotherapy even after organogenesis.<sup>11</sup>

Overall, the risk of teratogenesis following cancer treatment appears to be lower than commonly estimated from the available animal data. First trimester exposure to chemotherapy has been associated with 10–20% risk of major malformations.<sup>7</sup> This risk was found to be lower with a single chemotherapy agent administration compared to combination regimens.<sup>12,13</sup> Further risk reduction has been observed when anti-metabolites, which are considered the most teratogenic among the chemotherapeutic drugs, were excluded.<sup>12,13</sup> However, the existing information regarding the administration of chemotherapy during pregnancy should be extrapolated with caution since it was largely based on a collection of small retrospective studies and case reports. Furthermore, it included pregnant women who were treated with different chemotherapeutic regimens and covered long periods of time during which the treatment of cancer had changed.

Second and third trimester exposure is not associated with malformations but increases the risk for fetal or neonatal death, intrauterine growth retardation (IUGR) and low birth weight.<sup>7,9</sup> However, the IUGR and low birth weight are not associated with significant long-term complications and death rate is very low in these circumstances. Therefore, it seems that the advantage of treatment is clear and that multi-drug regimens can be administered during this period.

The decision to use chemotherapy during pregnancy should be weighed against the effect of treatment delay on maternal survival. If possible, chemotherapy should be postponed until the end of the first trimester. Of the different types of chemotherapy, anti-metabolites appear to be more teratogenic than other anti-cancer drugs.<sup>7,9</sup> If the administration of chemotherapy in the first trimester is essential, a therapeutic abortion should be strongly considered.

Delivery should be planned to 2–3 weeks following treatment to allow bone marrow recovery. Furthermore, neonates, especially preterm babies, have limited capacity to metabolize and eliminate drugs due to liver and renal immaturity. The delay of delivery after chemotherapy will allow fetal drug elimination by the placenta.<sup>9</sup>

## Supportive treatment

Up to 70% of cancer patients may suffer from nausea or emesis following anti-cancer chemotherapy and may require anti-emetic treatment such as meto-

clopramide, anti-histamines or ondansetron-based drugs. No association was found between treatment with these medications and congenital malformations in both animal models and humans.<sup>14,15</sup>

Pregnant women treated with anti-cancer chemotherapy, and especially patients with acute leukemia treated with high dose chemotherapy are at increased risk for infections including neutropenic fever and might be treated with antibiotics. The fetal safety of penicillins, cephalosporins and erythromycin is well established.<sup>16</sup> Aminoglycosides<sup>16</sup> and metronidazole<sup>17</sup> do not appear to be teratogenic, however this is based on more limited data. Quinolones, that cause arthropathy and tetracyclines that affect bone and teeth should be avoided during pregnancy.<sup>2,16</sup> Sulfonamides, similar to other folate antagonists have been associated with neural tube defects and cardiac malformations and should be avoided when possible.<sup>17</sup>

Beside bacterial infections, patients with severe neutropenia are prone to invasive fungal infections. The systemic antifungal drug with which there has been the most experience in pregnancy is amphotericin B. There have been no reports of teratogenicity attributed to this agent making it the antifungal drug of choice during pregnancy.<sup>18,19</sup> There is evidence to suggest that fluconazole exhibits dose-dependent teratogenic effects, however, it appears to be safe at lower doses (150 mg/day) [19]. There is a very limited experience with the administration of ketoconazole and flucytosine during pregnancy and these drugs have been shown to be teratogenic and embryotoxic in animal models. Therefore treatment with these agents should be avoided during pregnancy.<sup>18,19</sup>

The experience regarding the treatment of chemotherapy-induced neutropenia with granulocyte colony-stimulating factor is limited. However, so far no teratogenic effects were reported.<sup>2</sup>

## Long term fetal effect of the treatment of leukemia

The fact that the CNS continues to develop throughout gestation is a cause for concerns regarding the long term neurodevelopment outcome of children exposed to in-utero chemotherapy for different malignancies including leukemia. Childhood malignancy and long term fertility are other concerns in these children. Data regarding these issues are limited due to the rarity of pregnancy associated leukemia and the difficulties in long-term follow-up. A long term (up to age 6-29, average 18.7 years) follow up of 84 children born to mothers with hematological malignancies, including 29 patients with

acute leukemia, has reported normal physical, neurological and psychological development.<sup>20</sup> This study has partially addressed the issue of reproduction in that all offsprings have shown normal sexual development and 12 of them had become parents to normally developed children. Finally, there was no apparent increase in the risk of developing childhood cancer compared to the general population. This report was supported by a review summarizing 111 cases of children born to mothers with different malignancies treated with chemotherapy during pregnancy.<sup>21</sup> These children, who were followed up for different periods of time (1 to 19 years) had normal late neurodevelopment based on formal developmental and cognitive tests. In summary, the available data regarding later effects of anti-leukemia chemotherapy on children's neurodevelopment are limited and most reports used retrospective design in order to recruit a sufficient number of cases. However, the general impression based on the available data including the experience with multi-drug chemotherapy regimens given to patients with different malignancies, suggests that chemotherapy does not have a major impact on later neurodevelopment, fertility or malignant diseases.

### **The treatment of acute leukemia during pregnancy**

Acute leukemia is an extremely aggressive disease and is fatal unless treated promptly. There is evidence suggesting that treatment postponement until post partum is associated with an increased maternal mortality.<sup>22,23</sup> Therefore, following the diagnosis of acute leukemia, induction therapy with a carefully selected regimen must be administered as soon as possible.<sup>22</sup>

### **Acute myelogenous leukemia (AML)**

The usual protocol for the treatment of acute myelogenous leukemia consists of a combination of cytarabine with an anthracycline for induction, and various intensive combinations for consolidation therapy.

### **Induction therapy**

#### **Cytarabine**

The experience with the administration of cytarabine during pregnancy is limited. However, the fact that it is an anti-metabolite raises concerns regard-

ing its safety. Indeed, data from animal models suggest that cytarabine is teratogenic.<sup>24</sup> A review of 93 cases of pregnant women exposed to cytarabine alone or in combination with one or more therapeutic agents (thioguanine, doxorubicin, vincristine, and prednisone), for the management of acute leukemia reported 4 cases of limb malformations associated with 1st trimester exposure.<sup>9</sup> Other complications included 6 cases of intra uterine fetal death (IUFD), 12 cases of IUGR, 5 cases of transient neonatal cytopenias and two cases of neonatal deaths secondary to severe infections.

### **Anthracycline**

Anthracyclines are an integral part of regimens used for the treatment of many malignancies besides leukemias, including lymphomas, breast and lung carcinomas and soft tissue sarcomas. The experience with the treatment of anthracyclines during pregnancy is limited mostly to doxorubicin and daunorubicin. Idarubicin, which is more lipophilic, has an increased placental transfer and affinity to the DNA, and therefore may be associated with higher rates of adverse fetal outcomes and should be avoided during pregnancy. Since doxorubicin seems to be as effective as the other anthracyclines for the treatment of leukemia, it is the preferred drug during pregnancy.<sup>9</sup> Overall, the treatment with doxorubicin is considered relatively safe throughout pregnancy and is not associated with an increased risk for severe congenital malformations.<sup>9,25–28</sup>

Another concern regarding the treatment with anthracyclines during pregnancy is whether they are cardiotoxic to the developing fetus. A long term follow-up of 81 children whose mothers were treated with anti-cancer regimens including anthracyclines has shown no myocardial damage in both gestational and post-natal echocardiogram.<sup>26</sup> Another review of 160 pregnant women exposed to anthracyclines has reported 3 cases of cardiotoxicity, mainly in association with cumulative doses and the use of radiation therapy.<sup>29</sup> In 2 cases, 2nd trimester exposure to idarubicin was associated with a reversible cardiomyopathy, and in one case of third trimester exposure, cardiac damage was lethal.

### **Consolidation therapy**

Consolidation therapy protocols may include lower doses of cytarabine and anthracycline or different drugs such as etoposide. Experience with

**Table 1** ACUTE LEUKEMIA DURING PREGNANCY - TREATMENT AND OUTCOME.

Diagnosis	Reference	Treatment	No of patients	Pregnancy outcome	Maternal outcome
AML (not M3)	Niedermier, 2005 Chelgum, 2005 Aviles, 2001	ARA-C & anthracyclines ± Mit / Eto / DXM	47 pregnancies: 5 at 1st trimester 10 at 2nd trimester 13 at 3rd trimester 19 no data	33 term infants, 4 premature birth, 1 IUGR+VSD+dysmorphic features, 1 fetal demise, 7 therapeutic abortions, 1 unknown	27 CR 1 toxic death 19 no data
APL	Dilek, 2006 Chelgum, 2001	ATRA ± ARA-C & anthracyclines	3 at 1st trimester  2 at 3rd trimester	2 therapeutic abortions, 1 fetal demise 1 term infant, 1 premature baby, died a day after birth d/t pulmonary hemorrhage	3 CR  1 CR 1 died of intracranial bleeding on 22nd day of treatment
ALL (B & T cell)	Bergstrom, 1998 Molkenboer, 2005 Chelgum, 2005 Hansen, 2001 Aviles, 2001	Maintenance for ALL Combinations of: Induction: Pred, VCR, asparaginase, DNR, CPM, IT MTX Consolidation: CPM, 6-MP, ARA-C, VCR, L-asparaginase, IT MTX,	1 19 pregnancies: 5 1st trimester 4 3rd trimester 10 no data	spontaneous abortion at 1st trimester 10 normal infants 4 premature 5 abortions (1 missed, 1 spontaneous, 3 therapeutic)	7 CR 2 refractory disease 10 no data

ARA-C = cytosine arabinose, DNR = daunorubicine, IDA = idaubicine, ADR = adriamycine, VCR = vincristine, 6-TG = 6-thioguanine, MIT = mitomycine, Eto = etoposide, RBZ = rubidazone, DXM = daunoxome, Pred = prednisone, ATRA = all trans retinoic acid, MTX = methotrexate, IT = intrathecal, Aspa = L-asparaginase.

the topoisomerase inhibitors etoposide and teniposide is extremely poor and therefore their administration during pregnancy cannot be recommended.

## Summary

Forty seven cases of pregnancy-associated acute leukemia reported of which 5 were diagnosed and treated during the 1st trimester (Table 1).

Given the paucity of experience and that cytarabine is an anti-metabolite, the administration of induction chemotherapy during the 1st trimester must follow a strong recommendation for pregnancy termination. In the 2nd and 3rd trimesters treatment with cytarabine and doxorubicin should be instituted promptly. The available limited data suggest that this regimen may be administered safely after the 1st trimester (Table 1). However, a close fetal follow-up is essential, especially by fetal cardiac function monitoring and by assessing limb development. Since this aggressive chemotherapy treatment may cause severe complications, such as infections, nausea and cytopenias, an adequate supportive treatment is essential (see above).

Treatment of AML in relapse consists of high dose chemotherapy, bone marrow transplantation (BMT) or experimental drugs. None of these therapeutic options can be delivered during pregnancy.

## Acute promyelocytic leukemia (APL)

The induction therapy for patients with APL includes All Trans Retinoic Acid (ATRA) and chemotherapy (most commonly an anthracycline). As with all other vitamin A derivatives, ATRA exposure during the 1st trimester is associated with an extremely high rate (up to 85%) of teratogenicity, including severe neurological and cardiovascular malformations. It is commonly accepted that any administration of ATRA during the first trimester should follow pregnancy termination.

The administration of ATRA alone or in combination with an anthracycline during the 2nd and 3rd trimesters has been reported in several case-reports (Table 1).<sup>30–36</sup> These reports have demonstrated normal pregnancy outcome without congenital malformations. These limited data may suggest ATRA as a therapeutic option for pregnancy associated APL during the 2nd and 3rd trimesters, however, stringent fetal monitoring, with particular emphasis on cardiac function, is mandatory.

Acute promyelocytic leukemia is of special importance to the obstetrician because of its association with disseminated intravascular coagulopathy (DIC), which may severely complicate the management of pregnancy, labor and delivery. Patients should be closely monitored for clinical and laboratory manifestations of DIC.

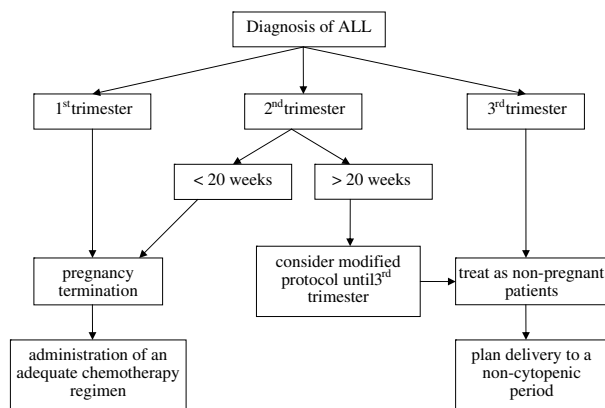
## Acute lymphoblastic leukemia (ALL)

Acute lymphoblastic leukemia is relatively rare among adults and therefore only 19 cases of pregnant patients with ALL have been reported (Table 1).<sup>37–40</sup> Since ALL is highly aggressive, adequate chemotherapy must be administered immediately after its diagnosis.

The scanty data regarding treatment of ALL during pregnancy does not allow firm recommendations. This issue is further complicated since methotrexate, which is a crucial component of most intensification protocols of ALL, is highly teratogenic. First trimester methotrexate exposure was associated with an increased risk of miscarriage. Exposure to high dose methotrexate (>10 mg/week) after the 1st trimester was associated with cranial dysostosis, delayed ossification, hypertelorism, wide nasal bridge, micrognathia and ear anomalies (aminopterin syndrome).<sup>41–49</sup> The risk for congenital malformations seems to diminish as pregnancy advances.

Nevertheless, according to the available data, we suggest that when the diagnosis is made during the 1st trimester, termination of pregnancy should be strongly considered followed by the administration of an adequate anti ALL regimen. ALL diagnosed during 3rd trimester should be treated as in non-pregnant women, however, both the mother and the fetus should be kept under close observation and delivery should be planned to a non-cytopenic period. The 2nd trimester can be roughly divided into two – before and after 20th week gestation. The first should be regarded as 1st trimester patients and termination of pregnancy should be considered. In the second group, treatment should be considered while the possible damage to the fetus is taken into account. Several chemotherapeutic regimens that do not include methotrexate have been suggested for treating this group.<sup>1,4,39</sup> However, the experience with these protocols, which are not usually used for treating ALL patients, is extremely limited and therefore they may be used as a short "bridging treatment" until 3rd trimester. A suggested algorithm for the treatment of pregnancy associated ALL is presented in Fig. 1.





**Figure 1** Treatment of acute lymphoblastic leukemia during pregnancy.

### Treatment of chronic myelogenous leukemia during pregnancy (CML)

The incidence of CML is about 1–2 per 100,000 cases per year accounting for 15% of adult leukemias.<sup>50</sup> The median age at onset of CML is in the sixth decade and only 10% of cases occur in women in childbearing age.<sup>51</sup> Traditionally, therapeutic options for CML included bone marrow transplantation, interferon alpha and chemotherapy. However, in recent years the treatment of the disease has evolved dramatically with the introduction of imatinib mesylate which has emerged as the treatment of choice for most patients with CML.<sup>52</sup>

### Imatinib mesylate

Imatinib mesylate (STI571, Gleevec, Glivec) is a tyrosine kinase inhibitor that entered clinical trials in 1998 and has since been shown to induce dramatic hematological and cytogenetic responses in CML patients in chronic and accelerated phase.<sup>53</sup> Several reports of animal models have suggested that imatinib may be teratogenic and therefore the present recommendation for women treated with imatinib is to use appropriate methods of contraception.

Twenty three cases of pregnant women with CML treated with imatinib have been reported in the literature.<sup>54–63</sup> Except for one woman with an accelerated disease, all patients were treated with imatinib for chronic phase. Five pregnancies were terminated prematurely: 4 by spontaneous abortion at the 1st trimester and 1 by a therapeutic abortion. The 18 pregnancies that ended on term, resulted in 19 healthy babies without significant congenital malformations (one infant had hypospadias but was otherwise healthy). In 13 of these

pregnancies imatinib treatment was discontinued as the pregnancy was distinguished (weeks 4–9 of gestation). In all patients but one,<sup>63</sup> the disease progressed following imatinib cessation and 11 women have required treatment with different therapeutic measures including interferon, hydroxyurea, leukapheresis,<sup>54,57,62</sup> or re-administration of imatinib after midgestation.<sup>55</sup> All 5 patients, treated with imatinib throughout pregnancy achieved and maintained complete hematological response.

The concentrations of imatinib and its active metabolite, CGP74588, were measured in maternal blood, placenta, umbilical cord blood and breast milk of two CML pregnant patients. The concentration was higher in the placenta than in the maternal blood while low or undetected in the umbilical cord. These findings suggest limited placental transfer in late pregnancy.<sup>54</sup>

There are opposing data on the impact of imatinib therapy cessation on the prognosis of CML patients. Most studies<sup>57,61–64</sup> have reported disease relapse following imatinib discontinuation and only a small fraction of the patients achieved complete remission after re-administration of imatinib. These observations raise the question whether cessation of imatinib treatment could be recommended for CML patients in complete remission on imatinib treatment who wish to conceive or maintain pregnancy. According to the limited data available it is still questionable whether patients with CML who become pregnant while being treated with imatinib should continue this treatment due to the high risk of disease progression following imatinib cessation or should they stop imatinib treatment and continue treatment with another drug. Nevertheless in patients diagnosed with CML during pregnancy, imatinib should not be the drug of choice for initiation of therapy due to the limited experience and the fear of congenital malformations. Imatinib treatment may be preserved for special cases such as for patients with accelerated disease who reject pregnancy termination or in those that fail or cannot tolerate the treatment with interferon.

Second generation oral tyrosine kinase inhibitors (eg: Dasatinib, Nilotinib) are now under research for CML treatment. No experience regarding their use during pregnancy is yet available.

### Interferon-alpha

Prior to the development of Imatinib mesylate, interferon alpha was the non-transplant treatment of choice for most patients with CML. Interferon alpha inhibits cell proliferation by its effect on protein synthesis, RNA degradation and possibly by

immune system modulation. It does not inhibit DNA synthesis. Due to its high molecular weight (19 kDa) interferon alpha does not cross the placental barrier to a great extent.<sup>65</sup> Neither mutagenicity in vitro nor teratogenicity have been observed in animal studies.<sup>66</sup>

The two major reports regarding interferon therapy during pregnancy<sup>67,68</sup> have described 40 cases (8 chronic myelogenous leukemia, 27 essential thrombocytosis, 2 hairy cell leukemia, 1 multiple myeloma and 2 hepatitis C virus carriers), 8 of them were treated during the 1st trimester. There were no cases of fetal malformation when interferon was administered as monotherapy. One fetus whose mother was treated with hydroxyurea at the time of conception had multiple congenital defects. Premature delivery occurred in 4 women and IUGR was documented in 6 newborns.

Several case reports of pregnant patients with CML treated with interferon have been documented.<sup>51,66,69–72</sup> None of them was associated with congenital malformation and all pregnancies resulted in healthy babies and normal maternal outcome. Due to the lack of evidence regarding any teratogenic effect of interferon it is considered a safe drug to be administered throughout pregnancy and therefore, it is the drug of choice for the treatment of CML during pregnancy.

## Hydroxyurea

Hydroxyurea is a cytotoxic drug that inhibits DNA synthesis. It was commonly administered to patients with CML prior to the introduction of imatinib mesylate. Although up to 90 percent of CML patients treated with hydroxyurea may experience clinical and hematological remission, this treatment is not curative, does not prolong overall survival, and only rarely results in attaining cytogenetic response.<sup>73</sup>

Several cases of hydroxyurea administration during pregnancy have been reported.<sup>74–81</sup> The main study described a single center experience of 31 patients and a review of another 19 women treated with hydroxyurea due to diverse hematological disorders (essential thrombocytosis, chronic myelogenous leukemia, sickle cell disease) during various terms of pregnancy.<sup>80</sup> Of the total of 50 cases there were 2 cases of IUFD (occurred in patients treated with hydroxyurea during the 1st trimester), 3 had minor malformations (hip dysplasia, unilateral renal dilatation, pilonidal sinus) and 9 cases of premature delivery. Second and third trimester exposure to hydroxyurea was associated with an increased risk of pre-eclampsia.

Based on the available experience it seems that the administration of hydroxyurea should be avoided during the 1st trimester. It could be reserved for patients in chronic phase who could not tolerate interferon alpha therapy during 2nd and 3rd trimesters.

## Leukapheresis

Leukapheresis may be used in the management of acute and chronic leukemias for rapid reduction of high white blood cells counts in patients with impending vascular occlusion. The experience with leukapheresis during pregnancy is extremely limited and is composed of only 2 case reports.<sup>81,82</sup> In both cases leukapheresis was the only treatment for CML and was well tolerated by the mother and fetus. CML patients treated with leukapheresis have an advanced disease and therefore require additional treatment. Nevertheless, it may be a possible short-term alternative to chemotherapy for pregnant patients near the end of the 1st trimester.

## Stem cell transplantation

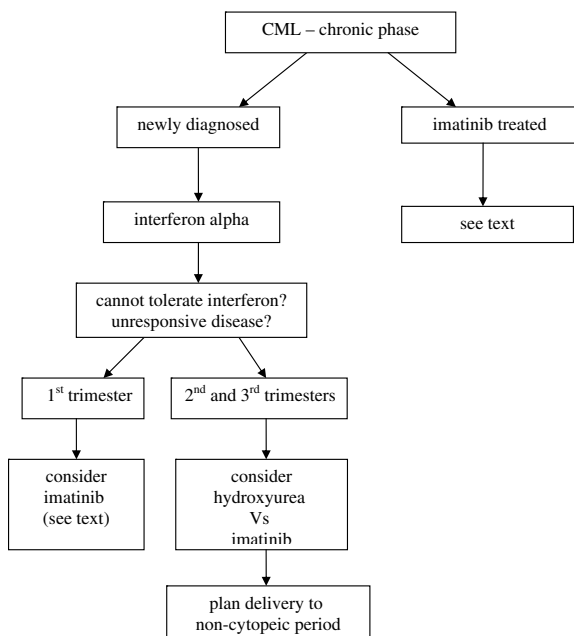
Allogeneic stem cell transplantation remains an important treatment option for patients with CML, particularly younger individuals who failed treatment with imatinib and have an HLA-identical donor. Given that there are no reports regarding stem cell transplantation in pregnancy and the aggressiveness of this treatment, it should be contra indicated during pregnancy.

## Summary

### Treatment of chronic phase

A suggested algorithm for the treatment of chronic phase CML is presented in Fig. 2. Treatment of CML is recommended as soon as diagnosis is attained and throughout pregnancy. Interferon alpha seems to be the only safe treatment during pregnancy and is therefore the treatment of choice in all trimesters. However, for patients treated with imatinib before conception continuation of imatinib may be considered due to the high risk of disease progression following its cessation. Still, the scanty data does not allow an unequivocal recommendation. Because of the relatively high rate of side effects many patients cannot tolerate interferon alpha treatment. When this happens during the first trimester, treatment with imatinib may be administered. In patients at the 2nd and 3rd tri-





**Figure 2** Treatment of chronic myelogenous leukemia during pregnancy.

mesters who cannot tolerate interferon alpha therapy, hydroxyurea is the most studied option and is considered safe after the end of the 1st trimester. Treatment with imatinib is another option that may be considered based on more limited data.

### Treatment of accelerated and blastic phase

Only one case of accelerate phase CML during pregnancy has been reported.<sup>57</sup> The treatments of choice for accelerated phase are imatinib and BMT. In the 2nd and 3rd trimesters imatinib treatment may be offered with a close follow-up of both the mother and fetus.

In cases of an unresponsive disease or blast crisis, patients should be treated as acute leukemia.

### Treatment of hairy cell leukemia (HCL)

Hairy cell leukemia accounts for approximately 2-3% of all adult leukemias in the western world. Due to its median age of diagnosis and the male predominance, HCL is very rare during pregnancy.<sup>83</sup> The disease is characterized by an indolent course which enables a delay of treatment. Of the 6 cases of pregnancy associated HCL that have been reported,<sup>84-88</sup> in 2 cases treatment was delayed until after delivery,<sup>85,87</sup> 2 patients

were treated with interferon alpha<sup>86</sup> and one patient with splenectomy.<sup>84</sup> In another case a medical abortion was performed.<sup>88</sup>

When treatment is indicated during pregnancy, interferon alpha is the treatment of choice. Splenectomy is reserved for those with failure of interferon alpha therapy.

### Treatment of chronic lymphocytic leukemia during pregnancy (CLL)

Chronic lymphocytic leukemia is the predominant leukemia among the elderly and affects men twice as often as women. The median age at diagnosis is 60 years, with only 10-15% of patients are younger than 50 years. Therefore, it has been very rarely associated with pregnancy.<sup>81</sup>

In contrast to acute leukemias, CLL is characterized by an indolent clinical course and therefore treatment can usually be delayed until post partum.<sup>89</sup>

Only four cases of pregnancy associated CLL have been reported.<sup>81,90-92</sup> In one patient with stage IV disease and severe leukocytosis (over 100000/ml) treatment was indicated during pregnancy and she was successfully treated with 3 sessions of leukapheresis.<sup>81</sup> Other two patients had infections during their pregnancy – one an episode of urinary tract infection and the other recurrent respiratory tract infections. All patients gave birth to healthy infants without congenital malformations.

There is no evidence regarding spread of CLL cells to the fetus. Two cases of placental invasion have been described,<sup>91,92</sup> but the clinical significance of these findings is not clear.

There are several options for the treatment of chronic lymphocytic leukemia. The most popular drugs are chlorambucil, corticosteroids and fludarabine.

### Chlorambucil

Data from animal models have demonstrated that exposure to chlorambucil during pregnancy has been associated with neural tube defects, limb malformations and renal hypoplasia.<sup>93-95</sup> Eight cases of pregnant patients exposed to chlorambucil have been reported in the literature.<sup>96-100</sup> First trimester exposure has been associated with congenital abnormalities including renal agenesis, ureteral malformations and cardiovascular anomalies.<sup>100</sup> The few cases of 2nd and 3rd trimester chlorambucil exposure have not been associated with congenital malformations.<sup>96</sup>

## Corticosteroids

Corticosteroids may be indicated for treating the autoimmune complications of CLL. The short acting agents – prednisone, prednisolone and methyl-prednisolone are metabolized by placental 11-hydroxygenase and therefore the fetus is exposed to approximately 10% of the maternal dose.<sup>101</sup> Studies on animal model have shown that antenatal exposure to glucocorticoids is associated with cleft palate and altered neuronal development, ultimately resulting in complex behavioral abnormalities.<sup>102</sup> Moreover, evidence exists suggesting that the administration of corticosteroids to pregnant women may be associated with several adverse effects including IUGR, low birth weight and increased infant morbidity.<sup>103</sup> Furthermore it seems that repeated courses of corticosteroids may have adverse long-term effects as it has been associated with hyperactivity later in childhood.<sup>103</sup>

The complications associated with the use of corticosteroids in a pregnant woman are the same as in non-pregnant patients. However, there may be several pregnancy-specific complications such as premature rupture of membranes and exacerbation of gestational diabetes and hypertension.<sup>104</sup>

A patient who has been treated with corticosteroids during pregnancy should be given “stress doses” of hydrocortisone for an emergency surgery, cesarean section, or prolonged labor and delivery. Neonates should be monitored for evidence of adrenal insufficiency and infections.<sup>105</sup>

## Fludrabine

The use of fludarabine for treating young patients with CLL has been gaining popularity lately. There are no reports regarding the administration of fludarabine during pregnancy. However, since anti-metabolites seem to be more teratogenic than other anti-cancer drugs, its use during pregnancy should be avoided if possible.

## Summary

Since CLL is an incurable disease with an indolent clinical course, treatment should be delayed unless the patient is symptomatic. Most patients can be monitored closely without treatment until delivery or disease progression. When treatment is indicated cytoreduction may be accomplished mechanically with leukapheresis. There is no information regarding cytotoxic treatment for pregnancy associated CLL. Chlorambucil is contraindicated

during the 1st trimester of pregnancy because of its teratogenicity. Its use may be considered later in pregnancy. Treatment of the auto-immune complications should be based on steroids, similar to non-pregnant patients.

## Breastfeeding and chemotherapy

The different chemotherapeutic agents vary in their concentration in breast milk and so dose-dependent as well as dose-independent effects of these drugs cannot be ruled out. Although it is unclear how much toxicity can be attributed to these drugs during lactation, most authorities recommend avoiding breastfeeding until at least 2 weeks following the completion of chemotherapy.<sup>1–3</sup>

## Ethical considerations

The diagnosis of leukemia during pregnancy raises complex ethical dilemmas. The fact that an adequate anti-leukemia treatment may be associated with poor fetal outcome including severe congenital malformations or death, leads to a potential maternal-fetal conflict. The dilemma is relevant especially in cases of acute leukemia, since the aggressiveness of the disease requires prompt administration of high dose chemotherapy, and is further complicated by the disparity between the limited available clinical experience versus the dramatic decisions that need to be taken.

Therefore, decisions about treatment of pregnancy associated leukemia must be case-specific. It is mandatory that the attending physician provides the pregnant patient and her family with all the available information regarding the different disease aspects including possible therapeutic alternatives and maternal and fetal risks. Every decision should be made together with the patient after careful consideration of both risks and benefits. However, when there is a clear risk to the mother, her safety must supersede fetal risk and an appropriate multi-drug regimen should be administered promptly following pregnancy termination.

## Future perspectives

There are no prospective studies on pregnant patients with cancer and data regarding the teratogenic effects of chemotherapy derives mainly from animal models. However, chemotherapy doses used in humans are lower than the minimum teratogenic doses applied in animals, making it difficult to extrapolate data from animals to humans.

Recently, there has been a growing interest in studying the effect of different drugs, including chemotherapeutic agents, on the placenta.<sup>106–108</sup> For example, the adverse effects of 6-mercaptopurine on the placenta has been documented with inhibition of both migration and proliferation of trophoblast cells in first-trimester human placental explants.<sup>106</sup> Placental perfusion studies can provide important information regarding both transfer and biotransformation of drugs in the placenta.<sup>109–111</sup> To date, these studies have been conducted using drugs not usually administered for cancer treatment. However, they can serve as a model for the assessment of placental transfer and the effect of cancer chemotherapy and thus add important information regarding fetal safety.

Finally, given the relative rarity of pregnancy-associated leukemia, there are only few medical centers or physicians that have gained experience in such cases. Therefore, there is a critical need for multi-center cooperation and a central registry that will collect and follow all cases of pregnancy-associated leukemia. This will facilitate conducting better epidemiologic studies and follow-up, and will enable physicians to assess more accurately the safety of the different anti-cancer treatments during the different stages of pregnancy.

### Conflict of interest statement

None of the authors has a conflict of interest or any affiliation with any organization with a financial interest in the subject matter in the manuscript. The manuscript is not sponsored by any company.

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