Cases of leukaemia in pregnancy in Slovenia during the period from 2006 to 2016 – How they were treated and literature review

Levkemije v nosečnosti v obdobju 2006–2016 v Sloveniji, zdravljenje in pregled literature

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Abstract

The incidence of leukaemia detected during pregnancy ranges between 1/10,000 and 1/100,000. Often, treatment with cytostatics needs to be initiated immediately following diagnosis. However, cytostatics are teratogenic to the foetus; therefore, before the initiation of treatment, all options need to be weighed and the most acceptable one chosen. This paper presents two cases, one involving acute myeloid leukaemia (AML) and the other chronic myeloid leukaemia (CML) detected during pregnancy; both were managed at the Ljubljana University Medical Centre. They represent the only two known cases occurring in the past 10 years in Slovenia.

A patient with AML of acute promyelocytic leukemia (APL) subtype was treated with daunorubicine and all-transretinoic acid (ATRA) at the beginning of her second trimester of pregnancy. Based on our experience, it appears that the current treatment recommendations for APL during pregnancy are realistic, feasible and above all safe for both the patient and the foetus.

In the case of the patient with CML, who came for her first evaluation just before delivery, prominent findings included marked leukocytosis of 335×10^9/L, along with thrombocytosis and splenomegaly. She rejected all treatment methods, primarily leukapheresis. In spite of all this, she gave birth to a healthy child, without complications during delivery. Due to her enlarged spleen and the resulting risk of its rupture, delivery was completed by caesarean section. Based on our experience, it can be concluded that it is not possible to give a recommendation on the level of white blood cell (WBC) count at which it would be beneficial for the mother and the foetus to initiate treatment with leukapheresis. It is also unclear what level of spleen rupture risk an attempt at vaginal delivery would pose for the patient in such cases. Since pregnancy in itself exacerbates predisposition to thrombosis, the question of how often the risk of a thromboembolic event during pregnancy is increased due to various types of leukaemia thus remains a mystery.

Izvleček

Incidenca levkemij, odkritih v nosečnosti, znaša od 1/10.000 do 1/100.000. Nemalokrat je ob odkritju bolezni z zdravljenjem s citostatiki potrebno začeti takoj. Citostatiki so za plod teratogeni, zato moramo pred pričetkom zdravljenja pretehtati vse možnosti in izbrati najbolj sprejemljivo. Predstavljamo primera akutne mieloične levkemije (AML) in kronične mieloične levkemije (KML), odkrita v nosečnosti, ki smo ju obravnavali v Univerzitetnem kliničnem centru v Ljubljani. Gre za edina primera v zadnjih desetih letih v Sloveniji.

Bolnico z AML, podvrsta akutna promielocitna levkemija (APL), smo ob začetku 2. trimesečja nosečnosti zdravili z daunorubicinom in all-transretinoično kislino (ATRA). Glede na našo izkušnjo

se zdi, da so priporočila za zdravljenje APL v nosečnosti realna, izvedljiva in predvsem varna za bolnico in plod.

Pri bolnici s KML, ki je prvič prišla k nam tik pred porodom, je bila v ospredju izrazita levkocitoza za 335×10^9/L, trombocitoza in splenomegalija. Zavračala je vse načine zdravljenja, v prvi vrsti levkoferezo. Kljub vsemu je brez porodnih zapletov rodila zdravega otroka. Porod je bil zaradi povečane vranice in posledične nevarnosti za njeno rupturo dokončan s carskim rezom. Na osnovi naše izkušnje lahko zaključimo, da ni moč priporočiti, pri kako velikem številu levkocitov je za mati in plod koristno začeti zdraviti z levkoferezo. Enako tudi ni jasno, kakšno tveganje za rupturo vranice v teh primerih predstavlja poskus vaginalnega poroda. Uganka ostaja tudi vprašanje, kolikokrat se zaradi levkemij različnih oblik poveča tveganje za trombembolični dogodek v nosečnosti, ki že sama po sebi nagiba k trobozam.

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1 Introduction

Leukaemia, both acute and chronic, is a rare and difficult event during pregnancy (1,2,3,4). Its incidence ranges between 1/10,000 and 1/100,000 pregnancies (1,2,5,6,7). Among malignancies in pregnancy, which develop in about 1/1000 pregnant women, leukaemia ranks about seventh, behind breast cancer, thyroid cancer, cervical cancer, malignant melanoma, Hodgkin's lymphoma and ovarian cancer (8). In the case of acute leukaemia (AL), treatment with cytostatics should be initiated immediately, because untreated disease shows rapid progression and is fatal. Naturally, cytostatics are harmful to the foetus; therefore, all options should be weighed before the beginning of AL treatment, and the most acceptable one should be chosen (1,2,3,4,9). If chronic leukaemia is detected during pregnancy, it is usually chronic myeloid leukemia (CML). Quite often its detection occurs accidentally during the early chronic phase of the disease; this means that CML treatment can wait until after delivery (1,2). In the event of a high WBC count, treatment of a pregnant CML patient is urgent due to the blood hyperviscosity syndrome (1,2,9). The available therapeutic options include treatment with leukapheresis and cytostatics (1,2,4,9). Two cases of patients, one with acute and chronic leukaemia detected during pregnancy are presented below. These are the only two cases that were managed in Slovenia during the past ten years.

2 Clinical case of an acute leukaemia patient

A 35-year-old patient fell ill with acute promyelocytic leukaemia (APL) in her 13^{th} week of pregnancy, exhibiting a characteristic chromosomal translocation t(15;17) and a PML-RARα fusion gene. Based on her blood counts upon disease diagnosis, namely WBC 1.6×10^9/L and platelets 6×10^9/L, the patient was classified into the medium risk group (10,11). Induction treatment of APL was initiated with all- transretinoic acid (ATRA) and an anthracycline cytostatic daunorubicine (without the addition of cyto-

sine-arabinoside (AraC)), in otherwise standard doses (10,11,12,13). After induction chemotherapy, hematological remission of APL was achieved and the patient continued with her first consolidation chemotherapy using the same combination of ATRA and daunorubicine. For continued treatment, ATRA was combined with mitoxantrone. During treatment, not only hematological remission of APL was recorded in this patient, but also a complete molecular remission of the disease. No copies of the PML-RARα oncogene were detectable with quantitative PCR analysis in the sample of the patient's bone marrow after completed treatment. Based on the test results, the patient completed her chemotherapy treatment in the 27th week of pregnancy and did not receive the planned final consolidation cycle of combined treatment. Until delivery, she continued her interval maintenance treatment with ATRA, without any adjunct chemotherapy.

Throughout this time, the patient was monitored by her obstetrician/gynaecologist. No developmental defects were noted in the foetus on ultrasound, foetal growth was also appropriate. Foetal heart function was monitored regularly and it was normal throughout the course of pregnancy. Two months after completed APL treatment, the patient gave birth at term by planned caesarean section based on an obstetric indication and the baby showed no structural developmental abnormalities. The delivery was uneventful and the newborn child's birth weight was appropriate for the gestational age (AGA). The latter finding indicates foetus normal growth in the uterus and good functioning of the placenta. An echocardiographic examination of the newborn following birth showed a structurally and functionally normal heart. Due to the mother's deficient lactation, the child was not breast-fed. After delivery the patient continued maintenance treatment of APL with ATRA at three-month intervals and has been monitored by the haematology outpatient office to this date. At the time of her latest follow-up, the blood count parameters were within the range of normal values and no PML-RARα oncogene copies were detectable in the bone marrow samples. The child's development has been uneventful and no abnormalities have been found to date.

3 Clinical case of a female patient with chronic leukaemia

During her fourth pregnancy, a 40-year-old pregnant woman was followed-up by her personal gynaecologist. During the first trimester, he found elevated WBC levels that significantly exceeded otherwise physiologically increased levels in pregnancy. He referred the patient to a haematologist and a tertiary perinatal centre, but she refused such examinations despite receiving ample explanations. The patient thus came to our centre for the first time in her 41st week of pregnancy, right before delivery. She was then diagnosed with CML involving a characteristic chromosomal translocation t(9;22) and the consequential BCR-ABL1 fusion gene. In the clinical status, enlarged spleen was prominent and measured five centimetres below the left costal margin. In the blood counts, there was notable leukocytosis of over 300×10^9/L, thrombocytosis of 566×10^9/L and normocytic anemia

with a haemoglobin value of 111 g/L. The patient had no subjective problems, and no clinical signs of hyperviscosity syndrome were found upon her clinical examination. Due to leukocytosis, we wanted to immediately start treatment with leukapheresis, but the patient persistently refused it. While we were trying to convince her, she went into spontaneous labour. In the blood counts, the values were: WBC 335×10^9/L, platelets 517×10^9/L and haemoglobin 104 g/L. Due to enlarged spleen, which was prone to rupture during delivery, the delivery was completed by caesarean section. The latter was uneventful, haemostasis was appropriate throughout the course of delivery, and bleeding was within the expected limits. The child was born without developmental defects and with an appropriate weight for the gestational age. Immediately after delivery, the patient started receiving chemotherapy with peroral hydroxyurea (HU) and had to discontinue breast-feeding. On the fifth day after delivery, she was discharged to home care. After her discharge from the Ljubljana Maternity Hospital, the patient was managed at the haematology outpatient office. After the WBC values decreased, HU was replaced with nilotinib. Due to still present thrombocytosis of over $1000 \times 10/^9$ L, which may increase the risk of a thrombotic event in the puerperium, acetylsalicylic acid was added at a small dose of 100 mg daily (1,4). Upon the patient's last visit at the hematology outpatient office two months after delivery, haematological remission of CML was noted. She later no longer returned for follow-ups at the haematology outpatient office and did not respond to any of our several invitations.

4 Discussion

The first case involved a patient with newly diagnosed AML of an APL subtype at the beginning of her second trimester of pregnancy. APL is a subtype of AML having an excellent long-term prognosis, as 80 to 90 % of patients can achieve remission and later cure (11). The APL treatment protocol differs from treatment protocols for other AML subtypes. This is because initially it does not include the addition of AraC to the anthracycline cytostatic (1,11,12); one exception to this rule is high-risk APL (1,11). In our case, the patient was classified in the medium risk group and therefore did not need AraC; this significantly affected further management of her pregnancy.

Antimetabolites, which include AraC, are the most teratogenic of all the different groups of cytostatics and primarily cause deformed extremities (1,2,3,4). When reviewing 81 described cases of AL treatment during pregnancy between the years 1990 and 2009, Vandenbriele et al. found that foetal developmental defects were present in 18 % of foetuses exposed to AraC and an anthracycline cytostatic, and in all foetuses exposed to a combination of AraC and 6-thioguanine (14). If at all possible, the use of AraC should therefore be avoided during the first and early second trimester, as foetal organogenesis is still incomplete (1,2,14).

The two crucial medications for APL treatment are ATRA and arsenic trioxide (ATO); not infrequently, a combination of the two is also used (1,13). ATO is extremely embryotoxic and foetotoxic, so it is not recommended during any period of pregnancy (1,2,4). The use of ATRA during the first trimester has been associated with a 20 % incidence of

developmental defects in the foetus (14). It causes neural tube defects, as well as defects of the heart, kidneys and thymus (1,2). At the same time, these data show a relative safety of ATRA use during the second and third trimesters (14).

Within the scope of induction treatment for APL, ATRA and/or ATO is/are always combined with an anthracycline cytostatic, most commonly idarubicine (10,11,13). During pregnancy, however, daunorubicine appears to be a safer option for the foetus than idarubicine, as the latter is more lipophilic and therefore more readily passes through the placental barrier into foetal circulation, having both embryotoxic and foetotoxic effects (1,2,3,4). If APL is diagnosed during the second trimester of pregnancy or later, as was the case with our patient, it seems more correct and less harmful to the foetus to initiate treatment with a combination of ATRA and daunorubicine (1,2,3). This is also how our patient was treated. Due to the cardiotoxicity of anthracyclines for the mother and foetus, it is essential to carefully record the cumulative dose of received anthracyclines (1,3). For example, our patient received 70 % of the permitted cumulative dose and gave birth to a healthy child with normal cardiac function. No other defects or deformities related to foetal development were found either.

AL represents the majority of leukaemia cases detected during pregnancy. Two thirds of all such cases involve myeloblastic AL, which was also the case in our patient (3). When AL is detected during the first trimester, it definitely needs to be treated immediately after diagnosis, not only to protect the mother, but also for the benefit of the foetus. The average survival rate of such patients without treatment is so low that the foetus would not reach viability even if treatment was postponed. Immediate treatment is thus essential, regardless of the stage of pregnancy and in spite of the known teratogenic effects of chemotherapeutic agents used for AL therapy. Due to the teratogenicity of the used medications, any pregnant woman treated during the first trimester of pregnancy should be offered the option of having an artificial abortion (1,2,4,9). However, this can be done only after remission of the disease has been achieved, because during the acute phase of the disease artificial abortion would pose a risk to the pregnant woman due to disseminated intravascular coagulation (DIC) (8).

Treatment of AL in pregnancy not only leads to an increased risk of congenital developmental defects in the foetus, it also increases the risk of many other complications during the perinatal period: spontaneous abortion, premature delivery, intrauterine foetal growth retardation, stillbirth, neonatal neutropenia and sepsis (1,2,3). Complications such as stillbirth and premature delivery are also more common in pregnant women with leukaemia who remain untreated. Therefore, not all complications can be attributed to treatment (2,3,4). Other potential causes include anaemia in pregnancy, uteroplacental circulatory disturbances resulting from lymphocytic aggregates, and placental infarctions resulting from hemorrhagic or thrombotic events. Prenatal monitoring of pregnancy in the case of diagnosed leukaemia should therefore include more frequent and detailed foetal status monitoring using ultrasound examinations and cardiotocography. In the absence of any signs of foetal distress or uteroplacental

insufficiency, AL treatment may be continued until term. Initiating iatrogenic preterm delivery in order to shorten foetal exposure to chemotherapy is actually more harmful to the foetus. This is because the negative effects of premature birth (including late preterm delivery after completed 34th week of pregnancy) exceed the potential negative effects of chemotherapy in this phase of pregnancy. It has been proved that the cognitive function of children born to pregnant women who needed chemotherapy during pregnancy depended primarily on their gestational age at birth and improved with longer gestation (15).

Newly diagnosed chronic leukaemia in pregnancy is less common than AL (1,2,4,9). As a rule, such cases usually involve myeloid leukaemia. The latter represents 10 % of all cases of leukaemia in pregnancy (2). Relatively safe therapeutic methods, which are not harmful to the foetus are available for the treatment of pregnant women with newly diagnosed CML (1,2,4). The first such method is leukapheresis, an alternative to chemotherapy, with the use of which it is possible to avoid the teratogenic effects of cytostatics (1,4,9). Interferon (IFN) alpha proved to be a safe drug and can be administered already during the first trimester. It does not inhibit DNA synthesis and because of its large molecular weight it also does not pass through the placenta into the foetal circulation (1,4). Among chemotherapeutic agents, hydroxyurea (HU), a DNA synthesis inhibitor, is used for CML treatment. In animals, it may cause malformations of the head, face and the spinal canal; it also inhibits foetal growth and may cause foetal death. Judging from reports on successful and normal pregnancies, in which HU was administered for treatment even in early stages of pregnancy, it appears that this medication is less embryotoxic in humans (1,4,9). Of all tyrosine kinase inhibitors (TKI) used to treat CML, the greatest amount of data is related to imatinib (1,2).

During early pregnancy, imatinib causes many congenital defects, such as premature closure of cranial sutures, scoliosis, shoulder joint abnormalities, double kidney, renal agenesis, pulmonary hypoplasia, omphalocele and other similar conditions (1,2,4).

Since imatinib does not cross the placental barrier, some believe that it can be used for treatment from the second trimester onward (1,4,9). However, there is no solid evidence to prove safe treatment of pregnant women with imatinib, as very few clinical cases have been described in the literature (4,9). Significantly less experience and data is available for the remaining, more recently developed TKI, such as nilotinib, dasatinib, bosutinib and ponatinib. Dasatinib crosses the placental barrier and can also be detected in foetal plasma. It has been reported that this medicine caused foetal hydrops and severe foetal cytopenia during the first trimester of pregnancy, but there have also been rare cases of normally completed pregnancies (1,2). To summarise, in pregnant female CML patients, the WBC count is maintained within the recommended limits using leukapheresis or IFN alpha, as both approaches are practically harmless to the foetus. Therefore, artificial abortion is not necessary even during the first trimester. Treatment with HU is not recommended during pregnancy and there is no solid evidence of imatinib's safety. Compared to imatinib, even less information is available on the remaining TKIs (1,2). In our case, the patient consented to CML tre-

atment only after delivery. Cytoreductive treatment with HU was initiated. Since HU is excreted into mother's milk, she did not breast-feed (1,2). While the child was born with an equinovarus deformity of the feet, this cannot be attributed to the consequences of treatment for the blood disorder, as it was initiated only after delivery.

In and of itself, the state of pregnancy can present a risk of spleen rupture if it is enlarged. There are several reasons for this. The first one is elevated cardiac output in pregnancy and the consequently increased splenic blood flow. The cardiac output increases early during pregnancy (between the 8th and 10th week of gestation) and further increases at delivery due to the autotransfusion effect of contractions. The greatest increase in the cardiac output and consequently splenic blood flow occurs immediately after delivery due to an increase in the right heart preload, with a release of venous stasis in the lower extremities as a result of uterine contractions. Other reasons for increased risk of splenic rupture during delivery in the presence of splenomegaly include pressure of the diaphragm due to the patient's pushing in the second period of delivery and various manipulations performed by the medical staff. In the case of splenomegaly, which is the result of chronic portal hypertension, according to the Slovenian guidelines, a planned caesarean section is chosen only based on obstetric indications (16,17). There is very little data in the literature on the risk of splenic rupture if it is enlarged within the scope of CML. One clinical case is described, however, in which a female patient having a spleen reaching 10 centimetres below the left costal margin gave birth by vaginal delivery and without any complications; the child was healthy, although rather small for the gestational age (18). In our case, the patient's enlarged spleen was five centimetres below the left costal margin. The risk of splenic rupture was assessed to be higher, as splenomegaly most likely had developed over a relatively short period of time. The decision on the method of delivery was made even more difficult by the late diagnosis and the finding of splenomegaly just before delivery. Therefore, after consultation with a haematologist, we decided to complete the delivery by performing a caesarean section. This proceeded without complications and the patient gave birth to a child of appropriate size for the gestational age.

In all types of leukaemia, the high leukaemic cell count increases the viscosity of blood and consequently also the likelihood of a thromboembolic event. This risk is not negligible, as pregnancy in and of itself is a prothrombogenic state resulting from the process of human evolution (2,9). On the other hand, a high platelet count, usually higher than 1500×10^9/L, may lead to the development of acquired vonWillebrand's disease, which increases the patient's predisposition to primary haemostasis disorders (19). Using leukapheresis with concurrent thrombopheresis, WBC and platelet counts can be reduced quickly (2,9). Taking into account data from literature, leukapheresis sessions are initiated when the patient develops clinical signs of hyperviscosity syndrome or when the WBC count exceeds the value of 100×10^9/L (1,2). With WBC count values above 100×10^9/L, the risk of stroke, hypoxia, deep venous thrombosis, placental insufficiency, low birth weight or prematurity of the baby is significantly increased (1,2,9). In our case, the pati-

ent's WBC count was much higher than 100×10^9/L and therefore treatment by leukapheresis sessions was clearly indicated. The patient, however, refused them.

Despite WBC counts of over 300×10^9/L and thrombocytosis of over 500×10^9/L at the time of delivery, she nevertheless gave birth to a healthy child appropriate for gestational age. The delivery was without any associated bleeding or thromboembolic complications. Because of our experience, a question can be posed as to whether the threshold WBC count value of 100×10^9/L, at which treatment with leukapheresis should be initiated, is perhaps set too low. This is because no scientific research is available that would substantiate the above-mentioned WBC count recommendations. Indications for leukapheresis also vary among individual centres, so it can be concluded that this recommendation is in fact based on the opinion of some authorities (20). Naturally, it is not possible to recommend changes in the currently valid recommendations, which are indeed taken into account in the majority of cases, solely based on our case.

Physiologically, leukocytosis is a normal phenomenon during pregnancy (21,22,23). The WBC count increases with time during pregnancy and reaches the highest levels in the third trimester. After delivery, the WBC count rapidly decreases and returns to normal levels by the sixth day following delivery (21). The natural benefit of the WBC count dynamics observed in pregnant women is unknown (22). A WBC of about 15×10^9/L is an expected laboratory finding towards the end of pregnancy, while at the time of delivery values of up to 30×10^9/L have been reported (23). In differential blood counts, neutrophilic granulocytes are predominant. Among mostly mature forms of WBCs, 1–3 % less mature cells can be found, primarily myelocytes and metamyelocytes, but this is not considered pathological (22). This is because the process involves bone marrow's adaptation to pregnancy, with accelerated erythropoiesis (22,23). On the other hand, it is known that the state of pregnancy inherently increases the risk of thrombosis (24). Leukocytosis, which is significantly less pronounced than was the case with our patient, is also one of the main risk factors for the development of thrombotic events in some myeloproliferative diseases, such as polycytemia vera (25). Physiologically speaking, the purpose of leukocytosis in pregnancy may be to prevent major blood loss during delivery.

In our case, the CML patient had five risk factors for thromboembolic events: a high WBC count, hyperviscosity syndrome, thrombocytosis, pregnancy as such, and caesarean section. In spite of antithrombotic protection with low molecular weight heparin and antiaggregation treatment with acetylsalicylic acid, this patient was also lucky not to have suffered a thromboembolic event during pregnancy or later, following delivery.

The management of this patient was also made more difficult by her negative attitude towards the diagnosis and treatment of her disease. Soon after delivery, she abandoned follow-ups at the haematological outpatient office, so that now she does not receive any medications for her chronic blood disease. It is not known what is happening with her today. Every few months, we try to invite her to come for her follow-up via telephone and telegrams, but all attempts to contact her have been unsuccessful.

5 Conclusion

Based on our experience, it can be concluded that the recommendations for APL treatment with ATRA and anthracycline cytostatics during pregnancy are realistic, feasible and above all safe, for both the mother and the foetus.

In the case of the CML patient, it can be concluded that it is not possible to give clear advice as to the level of WBC count at which it would be beneficial for the mother and the foetus to initiate treatment with leukapheresis. Without a doubt, this depends on the type of leukaemia and the experience of individual centres with leukapheresis in similar cases. It is also unclear what level of spleen rupture risk would be associated with attempted vaginal delivery in such cases, i.e. at what spleen size it would be safer to complete delivery by caesarean section.

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