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Case report

REPEATED THERAPEUTIC LEUKAPHERESIS - A SOLE TREATMENT DURING PREGNANCY AS A BRIDGE BEFORE TYROSINE KINASE INHIBITORS FOR A PREGNANT WOMAN WITH CHRONIC MYELOGENOUS LEUKEMIA – A CASE REPORT AND DISCUSSION

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ABSTRACT:

Objective: Chronic myelogenous leukemia (CML) is a disease, that in cases with high leukocyte numbers, is treated with hydration and cytoreductive therapy.

Materials and Methods: A 20-year-old female patient, during a routine examination for pregnancy, presented with elevated white blood cells (WBC) count (over 275x10^9/L) and splenomegaly without any complaints. The diagnosis of Ph-positive CML was confirmed by cytology and PCR [presence of p210 type *BCR::ABL1* [e13a2 (b2a2)] transcripts. Since she was in her 6th month of pregnancy, abortion or conventional treatment (tyrosine kinase inhibitors (TKI), chemotherapy and/or allogeneic haematopoietic stem cell transplant) were contraindicated due to the high risk for both the mother and the fetus. The patient was treated with two consecutive leukaphereses followed by weekly apheresis for about 3,5 months until the day of the delivery. Each procedure included the processing of 1000-1200 ml of whole blood with the separation of around 600 ml white blood cell concentrate and plasma.

Results: The patient's WBC count was kept between 170 and 270 x 10^9/L until childbirth, and immediately after delivery, imatinib mesylate therapy was initiated. A healthy male child with a weight of 2250 kg and height of 46 ñm was born. The mother achieved hematologic, cytogenetic and molecular remission within the next 6-9 months after initiation of tyrosine kinase inhibitor therapy.

Discussion: The classical treatment for CML includes tyrosine kinase inhibitors, chemotherapy and/or allogeneic haematopoietic stem cell transplantation. All of these approaches have teratogenic potential, and therapeutic schemes should involve contraception. In cases with existing advanced pregnancy, therapeutic leukapheresis is a valid option for controlling WBC counts until the delivery date. Despite the later initiation of TKI therapy, the deep molecular response is still present thirteen years after the initiation of therapy.

Keywords: Chronic myelogenous leukemia, cytapheresis, TKI, imatinib, CML, pregnancy,

INTRODUCTION

Chronic myelogenous leukemia (CML) is a pluripotent stem cell disease characterized by anemia, extreme blood granulocytosis with granulocytic immaturity, frequent thrombocytosis, and splenomegaly. In more than 95 percent of the patients, the Philadelphia (Ph) chromosome (reciprocal translocation between chromosomes 9 and 22) is found. The chronic phase without therapy progresses to an accelerated phase and transforms into acute leukemia (blast crisis) with median survival measured in months. [1] Conventional therapeutic options of CML include tyrosine kinase inhibitors, hydroxyurea, busulfan, interferon-based regimens and allogeneic hematopoietic stem cell transplantation. [1, 2] In cases of high leukocyte count, the treatment includes hydration and cytoreduction in order to avoid leukostasis or cytolytic syndrome.

CASE REPORT:

Medical history: In September 2008, a 20-year-old female patient in her sixth month of pregnancy was diagnosed with chronic Ph+ CML. At presentation, the patient did not have any complaints.

The physical examination didn't find any changes in the skin, lymph nodes, cardiovascular or respiratory system. The abdominal palpation was difficult because of the pregnancy. There were no pathological changes in the extremities.

Results of pathological tests and other investigations: Peripheral blood leukocyte count revealed leukocytosis (275x10^9/L) with blood smear analysis of 1% myeloblasts, 2% promyelocytes, 24% myelocytes, 16% metamyelocytes, 10% immature neutrophils, 38% neutrophils and 9% lymphocytes. The biochemical tests

showed elevated levels of lactate dehydrogenase (LDH). The diagnosis of Ph+ CML was confirmed by cytology and RT-PCR of peripheral blood cells (presence of p210 type *BCR::ABL1* [e13a2 (b2a2)] transcripts with expression corresponding to CML). A myelogram was not performed because of the pregnancy and the typical peripheral blood findings. The ultrasound examination revealed splenomegaly (the longitudinal size of the spleen was about 26 cm). The SOKAL score was 0.6 (low risk). Bone marrow morphological examination and conventional cytogenetics were carried out after the baby was born.

Treatment plan: The Expert Group for Leukemias in the Specialized Hospital for Active Treatment of Hematological Diseases accepted the diagnosis of Chronic myelogenous leukemia in the chronic phase and decided that the patient should be treated only by leukapheresis until the delivery. Manual cytapheresis was accepted as more appropriate because it needed only one vein access without inserting central venous line.

Methods: Manual cytapheresis was performed with "double–double kit" plasmapheresis bags (Baxter Fenwal) and a blood centrifuge (Heraeus Cryofuge 8000). Sedimentation was accelerated by the high molecular weight agent hidroxyethylstarch (HES, MW200 000, Fresenius Kabi), and the whole blood was centrifuged at 116 G force for 6 minutes. During each procedure, two liters of blood were processed, and 1100 ml WBC and plasma were removed and replaced with 2000 ml saline and 200 ml Human albumin (20%, 100 ml Human albumin Octapharma). Bags that contained white blood cells, red blood cells (RBC), plasma and HES (Fig. 1) were further subjected to spontaneous sedimentation for an hour at room temperature, and the residual erythrocytes were also removed (Fig. 2) to be returned to the patient. Each procedure included the processing of 1000-1200 ml of whole blood with the separation of around 600 ml white blood cell concentrate and plasma.

During the first hospitalization, the procedure was performed on two consecutive days. The WBC count decreased to 150 x 10^9/L and was controlled daily. After that, the patient was treated by leukapheresis once per week for about 3,5 months until the day of delivery. The patient's WBC count was kept between 170 and 270 x 10^9/L. Following the delivery, therapy with imatinib mesylate 400 mg p.o. was initiated.

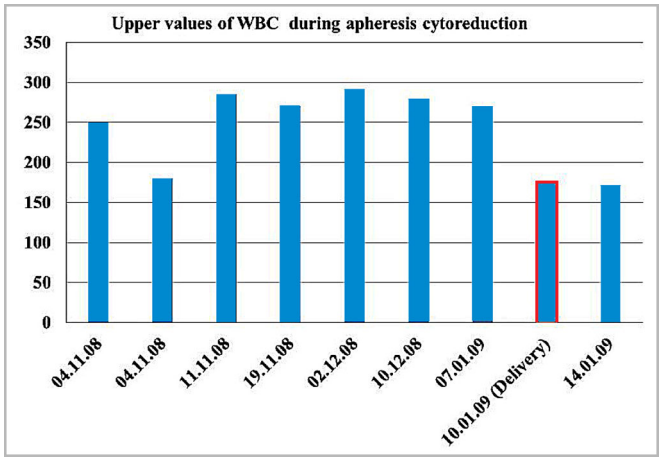
Fig. 1. Bags with white blood cells, plasma, residual red blood cells and HES, subjected to spontaneous sedimentation for different periods of time.

Fig. 2. A bag with white blood cells and plasma after RBC removal

RESULTS:

The WBC count after the first two procedures decreased to 150 x 10^9/L, and with weekly apheresis, it was kept below 300x10^9/L for about a 3.5-month period until the day of childbirth (Fig. 3).

Fig. 3. Initial white blood cells numbers prior to each cytapheresis procedure during therapy



A healthy male child (2.250 kg weight, 46 ñm height) was born by a Caesarean section. Imatinib monotherapy was initiated on the same day. Bone marrow aspiration of the mother performed a week later confirmed the diagnosis of myeloproliferative disease in the chronic phase.

Following the initiation of imatinib therapy and during the first month, the WBC count dropped to 30,6 x 10^9/L. Leukocyte count fell in the reference range during the second month of TKI treatment with normal hemoglobin and with moderate thrombocytopenia (79.9 x 10^9/L). Cytological investigation of the bone marrow after the second month of imatinib treatment still showed evidence of leukemia. Seven months after therapy with TKI, the blood tests were normal, and an initial 1 log reduction of *BCR::ABL1* transcripts in bone marrow specimens was registered at the 7th month of therapy. The complete cytogenetic response was achieved after the 12th month, and deep, complete molecular one after 23 months after imatinib initiation. The patient is still in complete cytogenetic and molecular remission and receives her therapy with tyrosine kinase inhibitors thirteen years later.

DISCUSSION

One of the complications of CML is hyperleucocytosis, which may lead to leukostasis and tumor lysis syndrome, both of which are life threatening conditions. This requires immediate reduction of leukocytes by treatment with leukapheresis or chemotherapy [1-3]. Our patient was in the 6th month of her pregnancy, which made its interruption very risky for the mother and fatal for the fetus. The high WBC number demanded cytoreduction to lower the risk of possible complications related to hyperleukocytosis. Cytoreductive therapy with chemotherapeutic agents (Hydroxyurea, Cytarabine, Busulfan) is myelosuppressive and could be toxic for the fetus . Other treatment option for CML with tyrosine kinase inhibitors during pregnancy may lead to adverse effects on fetal organogenesis and even fetal loss [4, 5]. A possible way to keep a lower WBC number, thus reducing the risk of leukostasis, is to perform mechanical cytoreduction using leukapheresis [6] as a safer for pregnancy approach [7-10]. A decision was reached to keep the WBC count low enough by initial reduction of the leukocyte number and its maintenance by weekly cytapheresis. The therapy with only available at this time, TKI (imatinib mesylate), which was given orally immediately on the day of delivery despite its later onset, led to complete hematological, cytogenetic and molecular response, which is maintained up to date, thirteen years later.

The conventional treatment with chemotherapy is potentially harmful to the fetus. Tyrosine kinase inhibitors are still new therapeutic modalities whose potential teratogenic and long term effects on the fetus have not yet been clarified. Leukapheresis is a relatively safe procedure and a valid option for controlling WBC counts in pregnant women with chronic myelogenous leukemia until delivery.

CONCLUSION

Our case confirms that cytapheresis is feasible and safe for controlling chronic myelogenous leukemia during its chronic phase when the initiation of chemo and/or TKI therapy is contraindicated.

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