

CASE REPORT

Induction with azacytidine followed by allogeneic hematopoietic stem cell transplantation in a Jehovah's Witness with acute monocytic leukemia

Hege Garelius, Sofia Grund & Dick Stockelberg

Section for Haematology and Coagulation, Department of Medicine, Sahlgrenska University Hospital, Gothenburg, Sweden

Correspondence

Dick Stockelberg, Department of Medicine and Oncology, South Alvsborg Hospital, 504 55 Boras, Sweden. Tel: +46 72 528 4126; Fax: +46 31820269; E-mail: dick.stockelberg@vgregion.se

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Key Clinical Message

We have used a hypomethylating agent instead of conventional chemotherapy to induce remission in a young Jehovah's Witness with acute monocytic leukemia to avoid severe myelosuppression and blood product support. The treatment was consolidated with reduced intensity allogeneic stem cell transplantation. This could be an alternative when transfusions must be avoided.

Keywords

Acute myeloid leukemia, allogeneic transplantation, azacitidine, Jehovah's Witnesses.

Case presentation

In April 2013, a previously healthy woman of 29 years, 8-week pregnant, was referred to our hematology unit. A suddenly appearing infected wound under her left armpit (Fig. 1) was the first sign of illness. She visited her General Practitioner several times and treatment with antibiotics did not help. She also felt unusually tired and dyspneic. Peripheral blood sampling was performed and a hemoglobin (Hb) level of 9.2 g/dL, an elevated white blood cell count (WBC) of $42 \times 10^9/L$ with 9% blasts, and platelet counts (Plt) of $52 \times 10^9/L$ were seen.

A bone marrow examination was performed that showed dominance of monocytic cells in different stages of maturation with a total of 64% monoblasts and promonocytes, the bone marrow morphology, thus consistent with Acute Monocytic Leukemia (AMoL). Monocytic origin of the blasts was confirmed by flow cytometry and cytochemical stainings. Cytogenetic analysis showed a very small hyperdiploid clone with an extra copy of chromosome 8 as the only aberration, confirmed with FISH. Molecular genetic analyses detected an FLT3-ITD mutation, a NPM1 mutation but a normal CEBPA gene, giving an intermediate risk profile. Clinical

examination of the skin showed several leukemic suspected skin manifestations in addition to the wound on the left arm.

At this point, we informed the patient and her husband about standard treatment with chemotherapy and allogeneic stem cell transplantation. However, she told that she was a Jehovah's Witness. According to Jehovah's Witnesses beliefs, blood consists of four main components: red blood cells (RBC), white blood cells, platelets, and plasma, and in addition many minor components including immunoglobulins, albumin, and stem cells. A committed Jehovah's Witness patient will not accept whole blood or its main components. However, whether minor components are acceptable or not is an individual decision [1, 2]. Reports concerning acute leukemia in Jehovah's Witnesses show that achievement of remission and even cure with intensive therapy is possible; however, deaths due to anemia or bleedings are frequent [3–5]. One way to reduce the risk of fatal complications has been to give a reduced induction [5–7] or treatment with a single agent [8]. Newer treatments, like the anti-CD33 antibody gemtuzumab ozogamicin have also been shown to be able to induce complete remission in patients with AMoL [9].

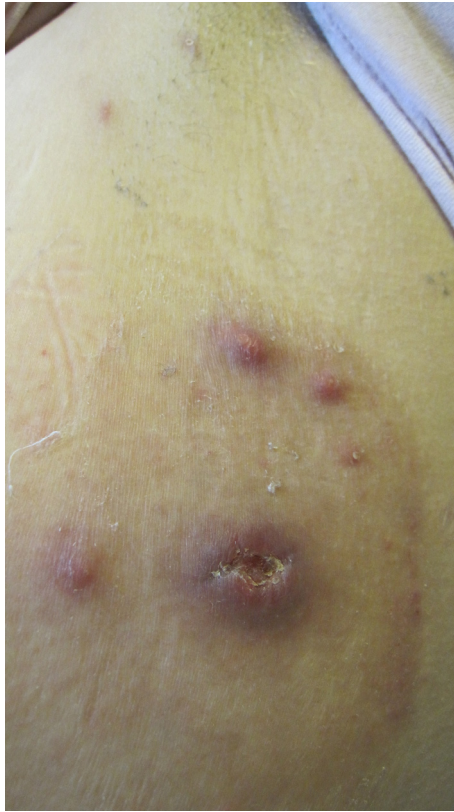


Figure 1. Infected wound under the patients left armpit.

After discussion with colleagues and the family, we decided azacytidine (AZA) treatment, in the dose of 100 mg/m^2 for 5 days every fourth week, as this regimen can induce remission [10, 11] but is less likely than standard induction to give rise to severe cytopenias. We started at once treatment with erythropoietin and iron supplementation and the patient received ciprofloxacin and fluconazole as prophylaxis against bacterial and fungal infection. Informed consent regarding treatment with chemotherapy without blood and platelet support was received from the patient; a particular emphasis was given to the increased risks of life-threatening bleeding, especially if the platelets dropped below $10 \times 10^9/\text{L}$. Before treatment started, the patient underwent an abortion with tranexamic acid given as prophylaxis against bleeding. Despite severe thrombocytopenia with platelet count of $10 \times 10^9/\text{L}$, she had no signs of bleeding. Hydroxyurea was given until abortion was completed and AZA treatment started.

At nadir after the first course of AZA, her Hb level dropped to $5.1 \times 10^9/\text{dL}$, the platelet count to $59 \times 10^9/\text{L}$ and WBC to $1.5 \times 10^9/\text{L}$ (Fig. 2). After 3 weeks, the platelets had normalized to $274 \times 10^9/\text{L}$, Hb was $8.2 \times 10^9/\text{dL}$ and WBC $2, 6 \times 10^9/\text{L}$. Hb levels could be maintained with

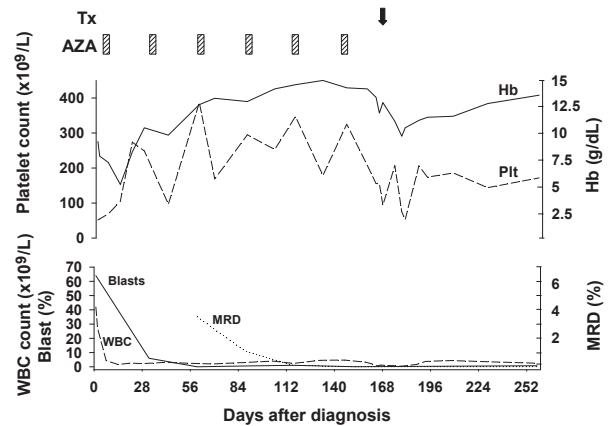


Figure 2. Serial blood counts, bone marrow blasts, and analysis of MRD during and after AZA treatment and allogeneic stem cell transplantation. Promonocytes are included in blast count. MRD was measured by flow cytometry in bone marrow. MRD was negative ($<0.1\%$) after five treatments. Abbreviations: Hb, hemoglobin; WBC, white blood cell count; Plt, platelets; MRD, minimal residual disease; AZA, azacytidine, Tx, allogeneic stem cell transplantation.

erythropoietin in a dose of 30,000 U weekly and iv iron supplementation until the iron levels were normalized. Erythropoietin was stopped after 2 months because of high Hb levels, and during the rest of the period of treatment with AZA, both Hb and platelets were in almost a normal range. Bone marrow aspiration after one course of AZA showed 6% bone marrow blasts (Fig. 2). After the second course with AZA, the bone marrow examination revealed complete remission. However, minimal residual disease (MRD) analysis with flow cytometry was still positive with 3, 5% cells expressing the original leukemic phenotype. The patient received in total six courses of AZA. During the last course, she experienced an allergic skin reaction at the site of injection, and also with hyperemia in several previous injection sites. This was treated with steroids and cetirizine.

Since treatment with AZA alone is unlikely to generate a durable remission [10, 11], allogeneic stem cell transplantation was planned as consolidation. The patient had five siblings of which none was HLA identical, but an unrelated donor with perfect match was found. At the pretransplantation bone marrow examination, no blasts or promonocytes could be detected. The MRD level was $<0.1\%$.

In order to reduce the risk of cytopenias requiring transfusions, the patient was treated with a reduced conditioning regimen with fludarabine 30 mg/kg for 6 days, busulfan 1 mg/kg for 3 days, and ATG (Thymoglobuline[®] ATG-Fresenius, Fresenius Medical Care, Sweden) 2 mg/kg for 2 days. She received peripheral stem cells from a male donor in a dose of $6.0 \times 10^6/\text{kg}$ $\text{CD}34^+$ cells. Her nadir of platelets was $53 \times 10^9/\text{L}$ on day +13 and absolute neu-

trophil count (ANC) rose to 0.3 on day +15. She was discharged after 27 days in the hospital. She received cyclosporine as GVH-prophylaxis, acyclovir 800 mg Q2 daily as antiviral prophylaxis, and Ciprofloxacin 500 mg Q2 daily until ANC was above $1.0 \times 10^9/L$. She was readmitted to hospital 1 month after transplantation due to severe headache, but no cause was found either by computer tomography or lumbar puncture.

At day 100 after transplantation, the patient was still in full remission with normal peripheral blood values. Chimerism at day 100 showed 3% recipient T cells in bone marrow. She had slight graft-versus-host disease in the mouth, genitals, and eyes that were treated with steroids.

Unfortunately, 5 months after the transplantation she relapsed with 40% blasts in the bone marrow. She was treated again with AZA in an attempt to reduce white blood count and blasts without affecting platelets and Hb level too much. In addition, she received hydroxyurea. Two and a half months after the relapse, she died in hospice.

Discussion

What have we learned from this exceptional case? As mentioned before Jehovah's Witnesses patients are known to not accept parts of blood transfusion products [1, 12]. This reduces the chance of cure of hematological malignancies, especially acute leukemia [7]. The relatively new drug azacytidine given to this young patient suffering from an acute monocytic leukemia with 64% monoblasts/promonocytes resulted in complete remission after two courses. After the 5th course, she was also MRD negative. We could keep her in remission for six cycles waiting for a donor to be found.

No blood products were given; she was treated only with erythropoietin and iron. Moreover, from the start of therapy until day 100 post transplant, she spent only 34 days in the hospital, 5 in the first weeks after diagnosis, and 29 days during/after stem cell transplantation.

What could we have done better? Normally, a patient in her age would have received a full conditioning regimen before transplantation. We were not willing to take the risk with a full conditioning regimen because no blood products were accepted. She did, in fact, not have a long cytopenic phase, but the regimen was probably too weak to prevent a relapse. Moreover, it took 6 months from start of treatment until we had a donor, a rather long time without any stronger chemotherapy but azacytidine. Her immunosuppression was maintained at a low level in order to enhance the graft-versus-leukemia effect. When the relapse was a fact, it was reduced even more.

This case report illustrates that patients with acute leukemia can be treated to complete remission with azacyti-

dine and stem cell transplantation without using blood products transfusion and with few days in hospital. It also represents the kind of very difficult dilemmas when the treatment options are few and the time is short before the leukemia relapses.

Conclusions

Hypomethylating agents like AZA followed by reduced intensity stem cell transplantation could be possible treatment in situations where blood products have to be avoided. However, the benefits from lower risk of severe cytopenias have to be carefully balanced against the higher relapse risk.

Consent

Informed consent was obtained from the patient for publishing this case report and accompanying images.

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Conflicts of Interest

None declared.

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