Long-term Suppression Of Bone Marrow With Prolonged Pancytopenia After Ibritumomab Tiuxetan In Jehovah's Witness Patient With Relapsed Follicular Non-hodgkin's Lymphoma

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Abstract

A 39-year old female Jehovah’s Witness patient presented with a relapse of B-cell follicular non-Hodgkin’s lymphoma. We had to avoid administration of any blood components as part of the treatment due to the conflict with the patient’s religious beliefs. Instead of administering a high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation we identified radioimmunotherapy with ibritumomab tiuxetan as the best therapeutic option in the circumstances. The treatment with ibritumomab tiuxetan led to severe and long-term inhibition of bone marrow with prolonged pancytopenia, extreme low count of hemoglobin level, platelets and neutrophils. During the entire post-treatment period the patient has refused to receive red blood cells, plasma or platelet transfusions. The patient has spent 11 months in cytopenia without life-threatening bleeding or organ failure and until now the patient is surviving in a complete remission with normal blood cell counts.

Introduction

Ibritumomab tiuxetan is a monoclonal antibody anti-CD20 labeled with yttrium radionuclide \(^{90}\)Y. It represents an effective radioimmunotherapy for patients with relapsed B-cell non-Hodgkin’s lymphoma [1,2]. The main adverse effect of ibritumomab tiuxetan is temporary myelosupression. In a group of 349 patients who were given a dose of 14.8 Mbq/kg (0.4 mCi/kg), 28% developed hematologic toxicity grade 3 with neutropenia (0.5-1.0x10\(^9\)/l), 52% with thrombocytopenia (10-50x10\(^9\)/l) and 14% with anemia (65-80g/l) [3,4]. Grade 4 toxicity was seen in 30% with neutropenia (9/l), 10% with thrombocytopenia (9/l) and 3% with anemia (9/l).

Case Report(s)

The 39-year old woman, Jehovah’s Witness had been diagnosed in May 2002 with a B-cell Non-Hodgkin’s follicular lymphoma, grade 2, CD20-positive, initial stage IV.A, with bone marrow infiltration of 10%, cervical, mediastinal, retroperitoneal lymphadenopathy and splenomegaly. In compliance with her religious beliefs the patient refused any treatment which would require blood transfusions or replacement of other human blood components. During the period from July 2002 to September 2003 she recieved combined chemotherapy CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with the anti-CD20 monoclonal antibody rituximab as first line treatment. Due to lack of effectiveness and persistent abdominal lymphadenopathy, and in order to avoid the administration of transfusion support, the patient was excluded from high-dose chemotherapy treatment followed by autologous peripheral blood stem cells transplantation. From September 2003 to October 2004 she underwent treatment with interferon alpha (at the time rituximab was not available for maintenance therapy). During the interferon treatment the marrow infiltration progressed up to 15%. Till January 2005 lymphadenopathy and splenomegaly increased. As the second-line treatment, from April 2005 to September 2005, she underwent, without blood transfusions, oral treatment FluCy (fludarabine, cyclophosphamide) and rituximab resulting in complete remission and persistent minimal residual disease in bone marrow under 5%. By June 2007 lymphadenopathy in the mesenterium, retroperitoneum, hepatosplenomegaly and new deposits in the spleen emerged. However, there was no finding of bone marrow infiltration. After a consultation with the patient we chose a salvage treatment option with DHAP (cDDP, Ara-C, DXM) at 50% reduced doses because of hematologic toxicity, followed by radioimmunotherapy with ibritumomab tiuxetan (90Y-anti-CD20) after the reduction of lymphadenopathy [1]. In the period from August 2007 to September 2007, after 2 cycles of DHAP, CT scan revealed regression of the lymphadenopathy to 25mm and extinction of the splenic deposits described previously. Shortly before administration of
ibritumomab tiuxetan a PET exam in November 2007 confirmed remission of the disease, without any area of pathological increased metabolism of 18FDG on both sides of diaphragm. On 30th of November 2007 ibritumomab tiuxetan was administered at a dose of 31,01 mCi (0.4 mCi/kg).

On the 32nd day after ibritumomab tiuxetan at a total dose of 1147,3 M bq (31,01 mCi) the patient developed severe pancytopenia without any symptoms of infection or bleeding. On the same day leukocytes decreased to 0,83x10^9/l, platelets to 10x10^9/l and mild anemia to 92g/l. Grade 4 neutropenia remained up to 67th day, thrombocytopenia to 81st and hemoglobin to 178th day after the administration of ibritumomab tiuxetan, grade 3 neutropenia to 92nd day, thrombocytopenia to 104th day and anemia to 252nd day. Extremely low level of hemoglobin was found on day 78 (17g/l). The patient survived more than 38-day period with hemoglobin level below 30g/l [Illustration 1,2]. At the time of severe myelosuppression one episode of febrile neutropenia occurred and was successfully treated with empiric antibiotic therapy (PIP/TAZO). No severe or life-threatening bleeding occurred, but some petechias appeared on the skin. The effect of severe anemia resulted in on physical inactivity of the patient. There was no organ failure or cardiac chest pain. Medication during hospitalization included haemostatic agents (etamsylat, pamba, vitamin K), gastrointestinal tract prophylaxis (proton-pump inhibitor, stool softener), cardiac vasodilatants (isosorbit mononitrate), substrates for haemopoiesis (folate, vitamin B6, iron supplementation), haematopoietic growth factors (pegfilgrastim, epoetin beta) and oxygen support. In case of life-threatening bleeding terlipresin and recombinant activated factor VII (rFVIIa) were prepared [7,8,9]. Rapid production of reticulocytes occurred from day 60. Sternal aspirate of bone marrow on 81st day established signs of regeneration of white and red blood cell lines. The patient was repeatedly instructed about risk of her decision. She was conscious with preserved intellectual skill and rational thinking, but consistently refused transfusion of erythrocytes, plateletes, fresh frozen plasma, or its derivatives, including human albumin. She preferred her own death rather than agreeing to substitution of blood components. She agreed with the application of haematopoietic growth factors (pegfilgrastim, epoetin beta) and recombinant clotting factor rFVIIa [7,8,9]. During the severe myelosuppression period patient was hospitalized for 69 days from January 4th 2008 to March 12th 2008. Recovery of the haemopoiesis was maintained until November 11th 2008 (WBC 3,76x10^9/l, NEU 1,84x10^9/l, Hb 105g/l, PLT 97x10^9/l) [Illustration 1,2.]. CT examination confirmed the complete remission of the disease, and the last blood count showed recovery of the functional bone marrow.

Conclusion

This case of a Jehovah’s Witness, suffering from relapsed B-cell non-Hodgkin’s lymphoma and unexpected long-term decline of hematological parameters after treatment with ibritumomab tiuxetan, is an interesting example of solving possible life-threatening complications, when an patient refuses blood products. This patient is now living in a complete remission after several months of life-treating myelosuppression without any blood cell supplementation.

Authors contribution(s)

The author declares that he has no competing interests.

References


Illustrations

Illustration 1

Serum levels of hemoglobin (g/l) and platelets (count x10^9/l).
Illustration 2

Leukocytes counts (count x10⁹/l) in peripheral blood.
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