Pathol. Oncol. Res. (2011) 17:141–143
DOI 10.1007/s12253-010-9276-4

Efficacy of Romiplostim in the Treatment of Chemotherapy Induced Thrombocytopenia (CIT) in a Patient with Mantle Cell Lymphoma

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Received: 2 February 2010 / Accepted: 6 May 2010 / Published online: 14 July 2010

Abstract Chemotherapy induced thrombopenia (CIT) is difficult to treat, as previous treatment options, including recombinant human thrombopoietin proved to be of limited efficacy. Here we report a case of a mantle cell lymphoma patient treated with intensive chemotherapy, who belongs to Yehova's witnesses and therefore did not accept platelet transfusions. At the time of severe thrombocytopenia (zero thrombocytes/ per mikroliter) and gastrointestinal bleeding, on day 13 following the start of hyperCVAD B chemotherapy, romiplostim treatment was given resulting in quick normalisation of the platelet count followed by thrombocytosis. Based on our observation in further studies modification of the dose and timing of romiplostim injection in CIT should be considered.

Keywords Chemotherapy · Lymphoma · Thrombocytopenia · Romiplostim

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Introduction

Chemotherapy induced thrombopenia (CIT) is difficult to treat, as previous treatment options including recombinant human thrombopoietin proved to be of limited efficacy [1]. Preliminary studies with the thrombopoietic agonist romiplostim could establish neither the optimal timing, nor the optimal dosage of the drug in CIT either in NSLCC or in lymphoma patients [2, 3]. Both studies failed to demonstrate efficacy regarding reduction of platelet nadir, or duration of grade 3 or 4 thrombocytopenia. Here we report a case of a lymphoma patient treated with intensive chemotherapy, who belongs to Yehova's witnesses and therefore did not accept platelet transfusions. At the time of severe thrombocytopenia (zero thrombocytes/ per mikroliter) and gastrointestinal bleeding romiplostim treatment was given resulting in quick normalisation of the platelet count followed by thrombocytosis.

Case Report

A 57-year-old man presented with a history of diarrhoea at his GP doctor. His previous medical history included repeated episodes of mild icterus, which have been attributed to beta-thalassaemia minor. A liver biopsy performed in 1970 showed normal liver architecture. He had not taken any medication for 6 months except for an ACE inhibitor prescribed because of slight hypertension diagnosed just before admission. A blood test was done and was found to be leukemic. He was admitted to hospital, where the clinical examination revealed generalized lymphadenopathy and important splenomegaly. B symptoms were absent. His haematological profile was as follows: haema-

tocrit : 40,0%, haemoglobin: 12.4 g/dl, RBC: 4,67 T/L, reticulocytes: 1, 8%, white blood cell count: 65.7 G/L (segmented neutrophils 9%, monocytes 1% mature looking small lymphocytes 87, prolymphocytes with one or two big nuclei 3%, some Grumprecht shadows in the peripheral blood smear, platelet count: 137 Giga/L. Serum biochemistry showed a normal level of lactate dehydrogenase (LDH): 339 U/L (normal range: 230–460 U/L). The C-reactive protein level was 1.7 mg/dl (normal range: 0–5.0 mg/L), the total bilirubin 61.7 umol/l (normal range 0.0–21.0 umol/l), direkt bilirubin: 10,6 umol/l, serum IgA 277.0 mg/dL (normal range: 70.0–400.0 mg/dL), serum IgG 1,000.0 mg/dL (normal range:700.0–1,600.0 mg/dL), serum IgM 257.0 mg/dL (normal range 40.0–230.0 mg/dL). In spite of normal kreatinine and GFR values the beta-2 mikroglobulin level was significantly elevated (4.5 mg/L, normal range: 0.8–2.8 mg/L). Flow cytometry of the peripheral blood showed 85% CD19+/CD5+ and partial CD23 expressing kappa monoclonal B-cells, while FISH studies performed on the peripheral blood revealed the presence of t(11;14) in 62% of mononuclear cells. The findings were consistent with the peripheral blood manifestation of mantle cell lymphoma. Staging gastroscopy showed only gastrooesophageal reflux. There was no evidence of HIV, hepatitis B or C infection.

Bone marrow biopsy revealed significant (35–40%) bone marrow infiltration with 53% t(11;14) positivity among the 200 analysed interphase nuclei, nevertheless cyclin D1 proved to be negative on immunohistochemical analysis. The percentage of Ki67+ cells was 10%. His chest radiograph was unremarkable. An enhanced CT of neck, chest, abdomen and pelvis was performed. Supraclavicular, left axillar, upper mediastinal, mesenterial lymphadenopathy and a huge splenomegaly (hilar diameter 9,7 cm) was found. The huge spleen caused some compression to the left kidney, otherwise the kidneys were structurally normal.

The final diagnosis was mantle cell lymphoma. The clinical stage was considered IV according to the Ann Arbour staging system. The mantle cell lymphoma international prognostic index (MIPI) was 3,5424 (low risk), while calculation of the simplified MIPI indicated intermediate risk disease. Chemoimmunotherapy was suggested to the patient, who, following detailed information fully accepted the necessity of this treatment. The patient however belongs to the witnesses of Yehovah, who refused to get blood and blood products. The suggested protocol for patients with advanced stages of MCL is induction therapy with HyperCVAD alternating with high-dose methotrexate and cytarabine (±rituximab) followed by autologous stem cell transplantation when the patient gets into remission. HyperCVAD A cycle at the end of September 2009 was uneventful. Rituximab treatment (375 mg/m2) was given on day 8 of the cycle following routine antihistamin and steroid pretreatment, nevertheless it was followed by severe cytokine release sydrome. On day 21 hyperCVAD A has been repeated to further reduce tumour burden, the treatment was uneventful. On day 28 a second course of rituximab treatment (375 mg/m2) was not followed by side effects any more. At this time point the spleen was palpable 6 cm below the left rib cage. On day 49 from start of chemotherapy hyperCVAD B cycle (high-dose methotrexate and cytarabine) was started, but because of fears from severe cytopenias, with 50% dose reduction and pegfilgastrim propylaxis 24 hours after chemotherapy. In spite of this dose reduction severe thrombocytopenia developed (from day 9 of hyperCVAD B cycle platelet count was less than 10 G/l) and rapidly declined further, reaching its nadir with unmeasurable value on day 13 of this cycle (Fig. 1). The severe thrombocytopenia was accompanied by gastrointestinal bleeding from day 9 to day 14. Because of the patient's refusal of blood products only volume replacement and erythropoetin were given. We applied for individual approach at the National Institute of Institute of Pharmacology to give romiplostim to the patient. On day 13 following the start of hyperCVAD B treatment, 1,000 μg romiplostim was given as a single subcutaneous injection. A rapid and steady increase in platelet count followed. The gastrointestinal bleeding quickly ceased. On the peak of the thrombocytosis inhibition of platelet aggregation with

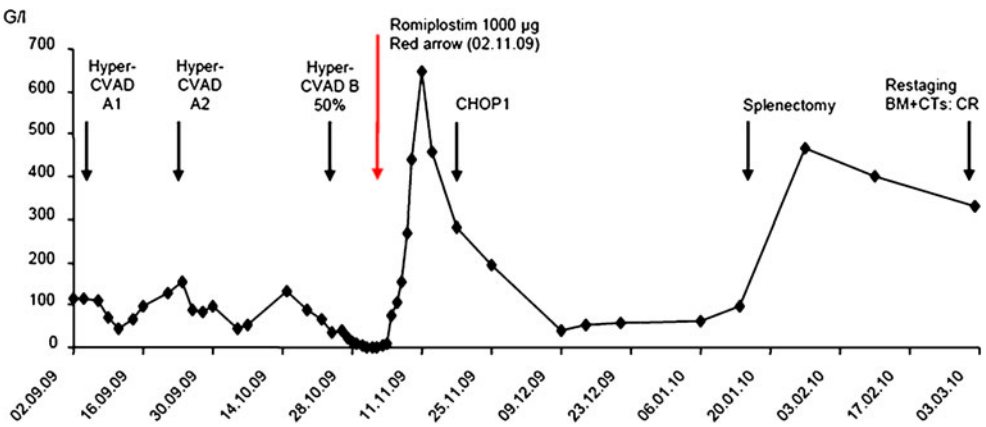

Fig. 1 Platelet values in the patient undergoing immunochemotherapy because of mantle cell lymphoma. 1,000 μg Romiplostim was given on day 13 following the first cycle of hyperCVAD B

the use of aspirin was performed. The platelet count reached it's maximum at 650 G/l, following which it gradually normalized, enabling us to continue chemotherapy.

Discussion

Treatment of patients with mantle cell lymphoma with high-dose chemotherapy requires intensive supportive treatment including antibiotics, hematopoietic growth factors, and the transfusion of blood and blood products. Our patient belongs to the witnesses of Yehovah, who, for religious reasons refuse to get blood and blood products. Without transfusions, patients with onco-haematological malignancies, who undergo high-dose chemotherapy develop severe life-threatening anemia and thrombocytopenia. Few patients with acute leukemias have been reported to implement agressive induction chemotherapy without blood support and literature on treatment results in patients with lymphomas seems to be even more scarce [4, 5]. In the desperate situation of chemotherapy—induced life threatening thrombocytopenic bleeding the use of romiplostim, a second generation thrombopoietic agent seemed to be safe and effective. The drug appeared to be well tolerable. The question arises what role the timing of the romiplostim injection (day 13 following start, day 7 following the completion of chemotherapy) in the apparent efficacy of the drug played. We have chosen to give the maximal dose of romiplostim (1,000 μg) used in dose finding studies in lymphoma patients with CIT (Fanale et al. 2009). In those studies a single subcutaneous injection of romiplostim was administered just 1 day after completing chemotherapy. In that study there was no evidence of a beneficial effect of romiplostim on the change in platelet nadir.

We attribute the quick increase of the platelet count (from 1 G/l to over 100 G/l within four days) as well as the ensuing thrombocytosis in our patient to the effect of romiplostim, rather than to spontaneous platelet recovery. Based on our observation in further studies modification of the dose and timing of romiplostim injection in CIT should be considered.

Conflict of interest None.

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