Use of interleukin-11 after autologous stem cell transplant: report of three cases and a very brief review of the literature

Thrombocytopenia remains one of the biggest problems in the administration of very high dose chemotherapy. While filgrastim and molgramostim have been shown to significantly increase the speed of leukocyte recovery in these patients, and recombinant erythropoietin has been also shown to decrease the duration of anemia. Up until now no cytokine has been useful to increase the speed of platelet recovery.

Interleukin-11 (IL-11) is a cytokine that stimulates hematopoietic stem cells as well as megakaryocytes, resulting in increased platelet production. It is produced commercially (Oprevelkin, Genetics Institute, Cambridge, MA, USA) by recombinant DNA in *Escherichia coli*. The commercial product is a 177 amino acid polypeptide. It is indicated for the prevention of severe thrombocytopenia and reduction of platelet transfusions in patients with non-myeloid malignancies. We report our results using Oprevelkin in 3 cases of autologous stem cell transplantation (ASCT) as well as a brief report of the literature.

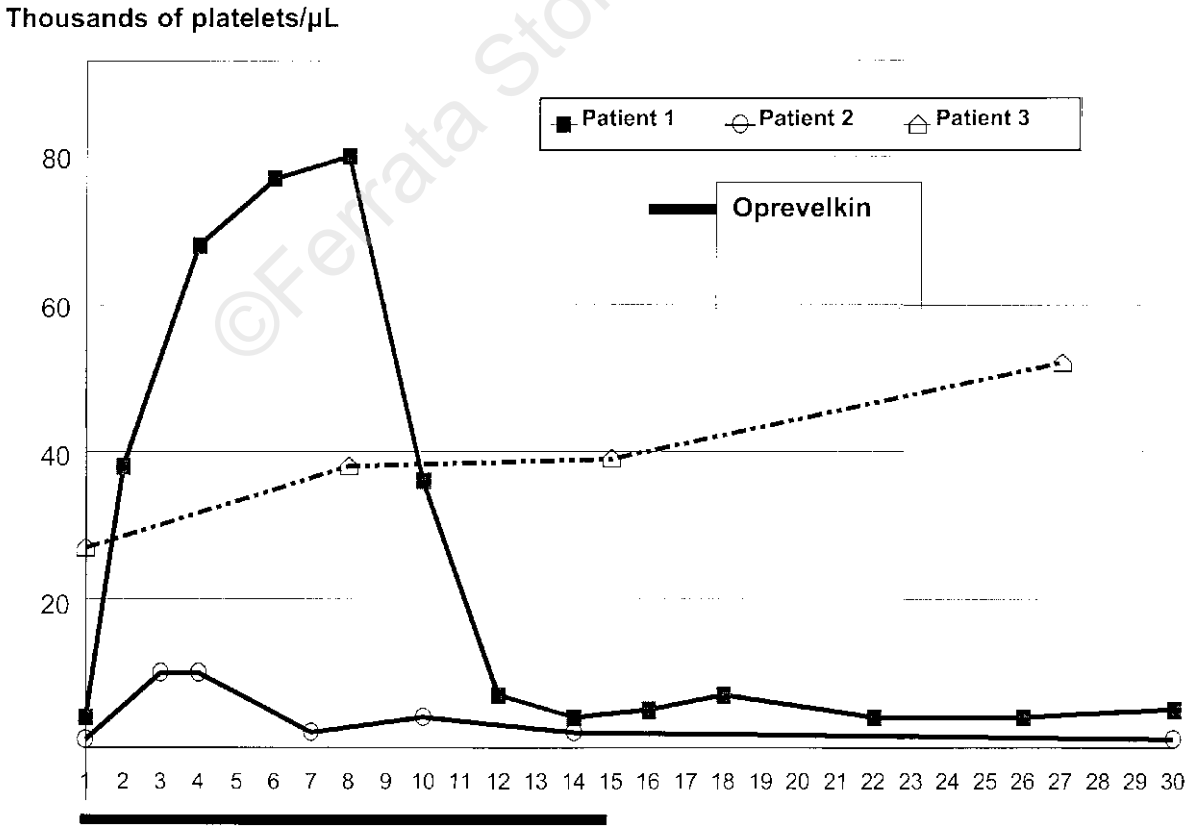
Patient #1. A 31-year old female with M3 ANLL received an ASCT after retinoic acid and standard consolidation therapy. She received 3.8 $\times 10^8$ mononuclear cells/Kg. Leukocyte and differential counts were normal by day +30, but remained heavily dependent on packed red blood cell (PRBC) units, requiring 3-4 units/month, as well as platelet units obtained by apheresis, (more than 15 units by day +100). By day +211, when she started receiving Oprevelkin, the platelet count was 4,000/µL.

Patient #2. A 19-year old male diagnosed with Ph$^+$ chronic myeloid leukemia in first hematologic remission, received an ASCT 11 months after his diagnosis using 21.1$\times$ 10^6 CD34$^+$ cells/Kg. By day +21 the patient had no signs of hematologic recovery, was heavily dependent on PRBC transfusions, had received more than 10 platelets units obtained by apheresis, his platelet count was 1,000/µL and WBC 100/µL. On day +23 he started 10 µg/Kg/day of granulocyte-macrophage colony-stimulatong factor 4,000 units/day of erythropoietin, and Oprevelkin.

Patient #3. A 47-year old female diagnosed with stage IIA IgG multiple myeloma, and in first complete remission after 3 VAD regimens, received an ASCT using 29.4 $\times$ 10^6 CD34$^+$ cells/Kg. Oprevelkin was started on day +78 with a WBC count of 3,500/µL, PRBC transfusion requirements were 1 unit/month and platelet count was 27,000/µL.

Mobilizations were performed using a single dose of 4 g cyclophosphamide, followed by 10 µg/Kg/day of filgrastim. Conditioning regimens were busulphan plus cyclophosphamide for the first two patients, and busulphan plus etoposide for patient number three. Oprevelkin was always administered 50 µg/Kg/day subcutaneously for 15 days.

Patient #1 had a very important increase in the platelet number, reaching 80,000/µL by day 8, but although Oprevelkin administration continued, the platelets dropped to 38,000/µL by day 10 and 4,000/µL by day 14. Patient #2 had a very modest transient platelet increase, reaching 10,000/µL by day 2 but falling back to 1,000/µL by day 7, with no further increase. In patient #3, a slow but maintained increase in platelet numbers



was seen coinciding with Oprevelkin administration, reaching 38,000 and 52,000 platelets/µL by days 8 and 27 respectively (Figure 1). No patient showed an increase in WBC or RBC counts. All patients complained of fleeting acute pain at the injection site. No other side effects were documented.

The rapid increase and decrease in platelet number seen in patient #1 during Oprevelkin administration was also observed, to a lesser degree, in patient #2. In the third patient, there was a slow but progressive increase in platelet numbers coinciding with the start of Oprevelkin, but this might also have been the result of a delayed engraftment.

Although cytokines are successfully used to manage neutropenia and anemia, the management of severe life-threatening thrombocytopenia during stem cell transplantation still depends very heavily on the use of platelet concentrates.

There is great interest in finding a clinically-relevant thrombopoietic growth factor. Among those being tested are thrombopoietin (TPO),[1] interleukin-6 (IL-6),[2] and IL-11.[3,4] All of them have proved to have some clinical usefulness.[5-7] Wiesdorf *et al.*[8] recently reported circulating levels of TPO, IL-6 and IL-11 measured from nadir until platelet recovery after bone marrow transplantation (BMT). Mean TPO and IL-6 levels showed an important rise followed by a fall preceding or coincident with the platelet nadir and recovery. In contrast, IL-11 levels remained constant throughout the whole course. This suggests that TPO and IL-6 function as regulators/stimulators of thrombopoiesis, while IL-11 does not appear to be a regulator of platelet production after BMT.

Imrie *et al.*[7] used Oprevelkin after ASCT in 6 cases of poor-prognosis Hodgkin´s disease. Although not a comparative study, the median time to a platelet count of >20,000/µL was similar to that in their own controls.

Vredenburgh *et al.*,[9] used Oprevelkin in patients undergoing ASCT for breast cancer. Eighty patients received either placebo or 25 µg/Kg. or 50 µg/Kg of Oprevelkin. In the placebo group, patients required an average of 12.4 platelet transfusions vs. 9.2 in the 25 µg/Kg(p=0.17) and 9.9 in the 50 µg/Kg Oprevelkin group (p=0.34). There was no significant difference between the groups in median number of days to platelet recovery. Based on our experience, as well as our review of the literature, we believe there is no clinical benefit from the use of Oprevelkin in ASCT.

José R. Borbolla, Manuel A. López-Hernández,° José DeDiego,° Mauricio González-Avante, ° Elvira Trueba,° Maria T. Collados#*

**Stem Cell Transplant Program and Centro de Investigación y Extensión de Ciencias de la Salud. Instituto Tecnológico y de Estudios Superiores de Monterrey, Monterrey, Nuevo León; ° Hematology Deptartment Centro Médico Nacional "20 de Noviembre", ISSSTE, México City; #Centro de Investigación y Extensión de Ciencias de la Salud, Instituto Tecnológico y de Estudios Superiores de Monterrey, Monterrey, Nuevo León; México*

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Correspondence: José R. Borbolla, M.D., Stem Cell Transplant Program, Centro de Investigación y Extensión en Ciencias de la Salud, Apartado 5091, Sucursal Tecnológico, Monterrey, Nuevo León, 64841 México. Phone/fax: international +52.8.3331121. E-mail: jrborbol@campus.mty.itesm.mx

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