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Case report

Effect of recombinant human interleukin-3 (rhIL-3) on persisting chemotherapy-induced thrombocytopenia

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A 57 year old woman with heavily pretreated advanced vaginal cancer (FIGO III) developed severe thrombocytopenia (7000/μl) with bleedings after chemotherapy. This patient was treated with recombinant human interleukin-3 (rhIL-3) after 26 platelet transfusions (25 pooled transfusions and one HLA-matched platelet transfusion) had not been effective. Increase of thrombocyte counts began 2 days after rhIL-3 therapy. Side-effects due to rhIL-3 administration (flu-like symptoms) were mild and could be treated effectively with paracetamol and clemastin. These data support first evidence for efficacy of rhIL-3 in chemotherapy-induced thrombocytopenia and may open new perspectives for its clinical application.

Key words: Chemotherapy, interleukin-3, thrombocytopenia.

Introduction

The major side effect of most anti-cancer drugs is myelosuppression. Death during myelosuppression is usually due to hemorrhage or sepsis. Hemorrhagic deaths are associated with thrombocytopenia and can be prevented by platelet transfusions in most cases.

Proliferation of hematopoietic cells is controlled by growth factors known as colony stimulating factors (CSFs). There are at least four growth factors that regulate proliferation and differentiation of myeloid cells, including granulocyte-macrophage (GM), granulocyte (G), macrophage (M) colony stimulating factor and interleukin-3 (IL-3, multi-CSF). IL-3 is a glycoprotein that promotes the proliferation and differentiation of multipotential hemopoietic stem cells and multi-lineage progenitor cells.[1] In comparison with other CSFs, IL-3 has been shown to be a potent stimulator of megakaryopoiesis.[2] Recent clinical studies with recombinant human IL-3 administered to patients with advanced malignancies, myelodysplastic syndromes, aplastic anemia or bone marrow failure have shown its multilineage stimulation of hematopoiesis *in vivo*.[3–6]

Here we report on a patient with vaginal cancer and severe chemotherapy-induced thrombocytopenia with bleedings, who could be treated successfully with IL-3 after 26 platelet transfusions had not been effective.

Case report

A stage III (FIGO) vaginal carcinoma with a tumor diameter of 5 × 4 cm with infiltration of the paracolpium and the right parametrium was subjected to primary combined radiotherapy (percutaneous dose: 50 Gy; afterloading 5 × 7.5 Gy) in a different hospital. The moderately differentiated squamous cell carcinoma (histological degree of differentiation: G2) exhibited substantial apocatastasis after the radiological treatment had been concluded. Seven months later, in the course of the oncological follow-up checks, it was discovered that the tumor had progressed considerably. As a result, the patient was sent to our hospital, where chemotherapy was planned. After three cycles of cytostasis with carboplatin (350 mg/m^2, d_1) and ifosfamid (1600 mg/m^2, d_{1-3}), remission was induced, so that operative therapy (colpectomy, retroperitoneal lymphonodectomy, hysterectomy and bilateral adnexectomy) became possible. Since the histological examination revealed right iliac lymph node metastases, chemotherapy was continued postoperatively. On the 14th day after the first postoperative cycle, the patient was admitted to hospital because of pronounced myelosuppression, accompanied by rectal bleeding and petechiae.

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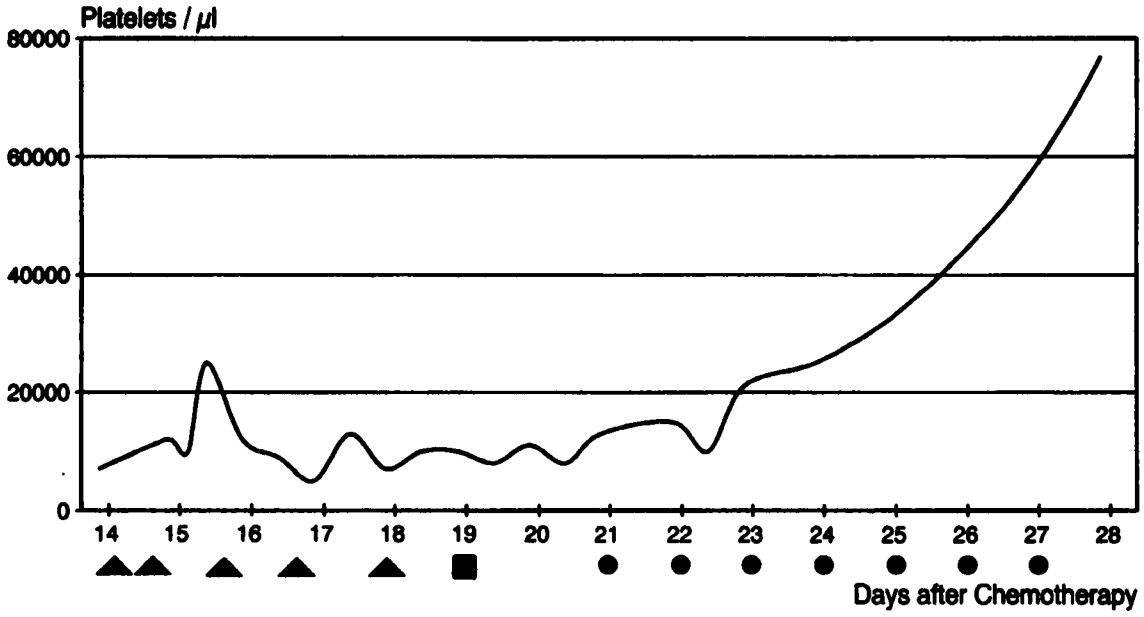

Figure 1. Course of thrombocytes under platelet transfusion therapy and IL-3 treatment observed in the individual case report. IL-3 was given subcutaneously daily for 7 days (5 µg/kg body weight, day 21–27). Time of therapy is given in days after chemotherapy. ▲, 5 × pooled platelets; ■, 1 × HLA-matched single donor platelets; ●, IL-3, 250 µg (5 µg/kg) s.c.

Laboratory parameters

Hemoglobin, 9.2 g/dl; thrombocytes, 7000/µl; leucocytes, 2000/µl. Coagulation parameters and electrolytes within the normal range.

No substantial increase in the thrombocyte count (12 000/µl) was achieved even after the five platelet transfusions, so that, when the thrombocyte count continued to drop steadily afterwards (to as few as 5000/µl), 21 further thrombocyte concentrates were transfused. Since the thrombocytopenia persisted for 6 days despite the 26 platelet transfusions (Figure 1) and the rectal bleeding continued, it was decided to adopt an interventional therapy by administering recombinant human (rh) IL-3 (Sandoz AG, Nuremberg, Germany) subcutaneously, at a dosage of 5 µg/kg body weight.

The decision in favor of this treatment was based on the successful use of IL-3 in an earlier prospective study of our group,[10] the results of which had been supported by a subsequent clinical trial—which has not yet been completed—on ovarian cancer patients treated with chemotherapy. The IL-3 treatment was started 2 days after the unsuccessful platelet transfusions, after the medication had been ordered from the manufacturing company for this purpose in order to treat the individual case described here, and after the patient had given her consent.

Whereas the thrombocyte counts in the course of the platelet treatment had been between 5000 and 15 000/µl (apart from a single count of 25 000/µl), an increase in the thrombocyte count to 21 000/µl was observed 2 days after the beginning of the IL-3 therapy, which continued during the 7-day therapy with this hematopoietic growth factor, rising steadily to a thrombocyte count of 77 000/µl (Figure 1).

After the conclusion of the IL-3 treatment, the thrombocyte count increased to 320 000/µl, then dropped to 240 000/µl during the further follow-up checks and then remained on that level (Figure 2).

Side effects of the IL-3 therapy

Redness at the injection site, temperature up to 39.5°C and headache were seen. It was possible to control these side-effects well with the antihistamine clemastin (Tavegil®, 3 × 1 tablet @ 1 mg/day) and with paracetamol (2 × 1 tablet @ 500 mg/day).

When the leucocyte count dropped to 700/µl (day 15), a single dose of 300 µg G-CSF (Neupogen®, Amgen) was administered subcutaneously, which resulted in a substantial leucocyte increase (up to 3200/µl on the 17th day after the chemotherapy), so that no further treatment with G-CSF was necessary.

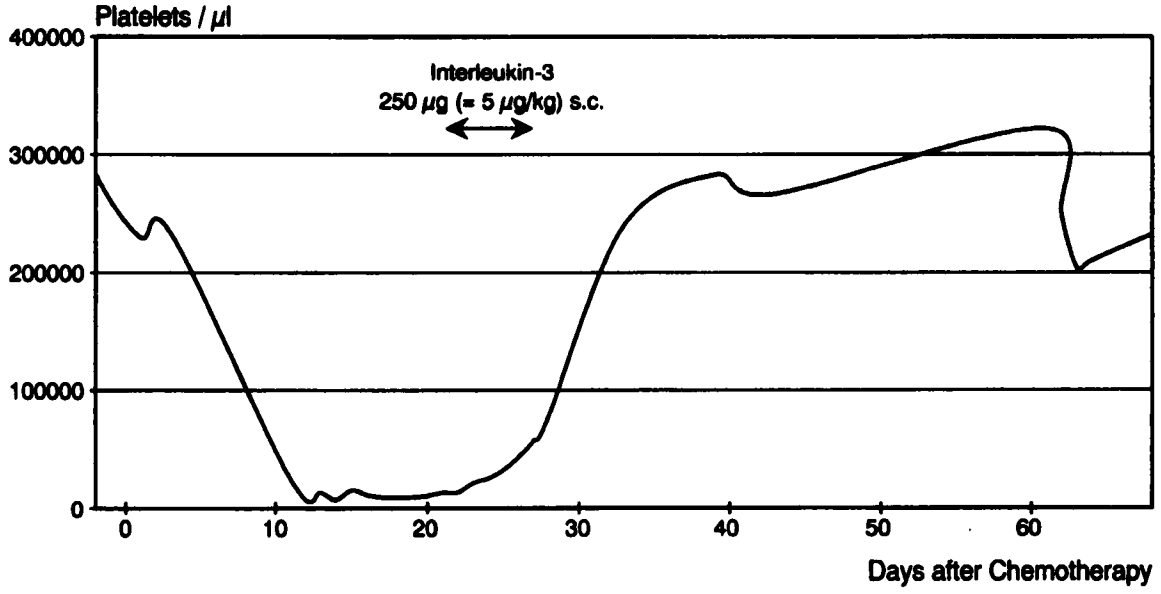

Figure 2. Course of thrombocytes before, during and after therapy with platelets and IL-3 (10 week follow-up).

Discussion

Proliferation, differentiation and functioning of hemopoietic cells are regulated by a number of cytokines. During the last few years much effort has been undertaken to characterize and clone hemopoietic growth factors and to introduce them into clinical trials.[6] Some of these growth factors, such as erythropoietin (EPO), G-CSF and GM-CSF, have already been used with success to treat cytopenic patients. IL-3, a product of activated immune cells, has recently been cloned and introduced in clinical trials.[3–5,7,8–10] Patients suffering from aplastic anemia, myelodysplastic syndromes or chemotherapy-induced myelo-aplasia received rhIL-3 at a dosage of 30–500 µg/m^2. The majority of the patients showed a dose-dependent increase in platelet counts.[3–6,9]

In the case presented here, we particularly focused on the question of whether persisting chemotherapy-induced thrombocytopenia can be treated with IL-3 after platelet transfusions had not been effective in a life-threatening clinical situation.

In our opinion, the sharp rise in the thrombocyte count after IL-3 application is a synergistic effect of spontaneous regeneration and the stimulation of megakaryopoiesis by IL-3. The contribution of the IL-3 effect in this connection cannot be quantified with certainty. The efficacy of IL-3 is nevertheless supported by the results available so far from the following studies:

(i) The efficacy of IL-3 with regard to the possibility of stimulating megakaryopoiesis *in vitro* has been demonstrated.[11]
(ii) Preliminary clinical trials on the use of IL-3 in support of chemotherapy in patients with ovarian cancer show that IL-3 is effective *in vivo*.[9,10]
(iii) In these cases, the effect is dose-dependent.[9,10]

IL-3 may have played a role in the case presented here, but it could be coincidental with the recovery after carboplatin therapy as well.

Conclusion

We conclude that myelosuppression which can be foreseen by the physician as a side-effect of chemotherapy can represent an indication for the administration of hematopoietic growth factors. IL-3 is a novel and unique growth factor under clinical investigation. Its clinical use can offer new strategies in the treatment of cytopenia, especially in cases with severe thrombocytopenia.

Hematopoietic growth factors could reduce the need of transfusion with blood and its components, especially after transfusion therapy has become more critical with regard to the risk of infections and allergic reactions.

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