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CASE REPORT

Romiplostim overcomes refractory secondary immune thrombocytopenia in a patient affected by serous ovarian carcinoma

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Abstract Immune thrombocytopenia (ITP) is an autoimmune disorder that occasionally arises with neoplasms. Although often sensitive to first-line treatment, a refractory thrombocytopenia may lead to a difficult management of the patient. A patient with primary ITP who successfully underwent surgery and chemotherapy with immunoglobulins and dexamethasone for ovarian cancer has recently been reported. We report on a 71-year-old woman who developed refractory secondary ITP concomitant with an advanced serous ovarian carcinoma. The ITP responded only to the thrombopoietin receptor agonist romiplostim with an uncommon threshold effect, enabling both palliative surgery and histological diagnosis. Although thrombopoietin receptor agonists might be useful in some circumstances, their safety and efficacy for cancer patients must still be determined. Well-designed clinical trials are urgently needed to resolve this issue.

Keywords Romiplostim · ITP · Ovarian cancer

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder due to both enhanced destruction and impaired production of platelets. Glucocorticoids and intravenous immunoglobulins (IVIG) are effective for most patients, but most relapse and require splenectomy or other second-line treatment [1]. Occasionally, ITP occurs in patients with solid tumors, as recently reported by Wakana et al. [2]. We report on a refractory secondary ITP associated with advanced ovarian serous cancer that responded only to high doses of the thrombopoietin receptor agonist (TRA) romiplostim.

Case report

A 71-year-old woman started complaining about abdominal pain and distension in March 2011. One month later, she was hospitalized with acute dyspnea and a massive left pleural effusion was found on chest X-ray. Blood count was normal. Computerized tomography scan revealed a 5 cm solid mass arising from the right ovary, ascites, and peritoneal carcinomatosis in the pelvis and upper abdomen. The CA-125 level was 2185 U/ml. Therefore, an ovarian cancer with peritoneal dissemination was suspected, but cytological examination of both pleural and ascitic fluid was negative. Surgical intervention was scheduled, but a few days later deep isolated thrombocytopenia (0.5×10^4/mm^3) was discovered. Blood smear showed no morphological abnormalities and laboratory coagulation results were normal. A diffuse purpura appeared, followed by recurrent epistaxis and gingival bleeding. Heparin prophylaxis was temporarily stopped, but thrombocytopenia and bleeding persisted. Serology for HIV, HCV, CMV, and parvovirus B19, and stool antigen test for *Helicobacter pylori* were negative. Bone marrow histology excluded metastatic disease but revealed an increased number of normal megakaryocytes. Thus, the patient was diagnosed

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with ITP. Both IVIG (1 g/kg/day for 2 days) and dexamethasone (40 mg/day intravenously for 4 days, 2 cycles) were ineffective (higher platelet count $0.7 \times 10^4/mm^3$). Splenectomy was excluded because of the risk of major bleeding during surgery. We informed the patient about the lack of feasible licensed therapeutic alternatives, about the approval of the TRA romiplostim for chronic primary ITP, and about its efficacy, safety, and side effects in such a setting and obtained her written informed consent to use romiplostim. The start dose was 1 μg/kg subcutaneously; this was then increased by 1 μg/kg/week until the platelet count was $>5 \times 10^4/mm^3$. No improvement was achieved with doses ≤4 μg/kg. Platelet count began to increase ($2.9 \times 10^4/mm^3$) on use of 5 μg/kg; 6 μg/kg resulted in $5 \times 10^4/mm^3$ and platelet count finally became normal (Fig. 1). Dose remained 6 μg/kg/week (median dose during the whole treatment, 6 μg/kg; total weeks of treatment, 11) and heparin prophylaxis was restarted. Performance status worsened, thus we excluded surgery with cytoreductive intent. However, the patient had clinical and radiological findings of bowel obstruction, therefore she underwent surgery with palliative and diagnostic intent. Laparotomic exploration revealed ovarian carcinoma extensively infiltrating pelvic organs and bowel with gross carcinomatosis and peritoneal metastases >2 cm in the right upper abdomen (Stage IIIC according to FIGO classification). Neither enlargement nor macroscopic involvement of the spleen was detected during surgical investigation, supporting the immune-mediated nature of thrombocytopenia. Surgical palliative relief of the intestinal obstruction was technically precluded by the diffuse neoplastic involvement of the entire small bowel with massive mesenteric infiltration. Multiple peritoneal biopsies were taken and definitive histological analysis revealed peritoneal locations of primitive serous ovarian carcinoma, poorly differentiated (G3), and cytological findings for peritoneal fluid revealed neoplastic ascites. Post-surgery laboratory results were: leukocytes $0.84 \times 10^4/mm^3$, hemoglobin 10.2 g/dl, and platelets $19.8 \times 10^4/mm^3$. A transitory increase of d-dimer (352 μg/l) without fibrinogen consumption (265 mg/dl) consistent with the surgical injury was also found. Partial removal of ascitic fluid led to an improvement of symptoms, but a week later it recurred and increased. Two days later a fever (39 °C) with bilateral pleural effusion developed. Laboratory results revealed leukocytosis ($1.56 \times 10^4/mm^3$), mild anemia (10.9 g/dl), and normal platelet count ($22.6 \times 10^4/mm^3$). Despite supportive care and empirical antibiotic therapy, the fever worsened and blood pressure decreased, leading to fatal septic shock 10 days after surgery.

Discussion

Although most commonly linked with hematologic malignancies, ITP has been reported in association with solid tumors also [2–5]. Two different associations are possible: pre-existing ITP in patients who develop a tumor and newly diagnosed ITP which arises concomitant with the neoplasm. In the latter setting, where a cancer-induced immune deregulation is conceivable, the diagnosis is secondary ITP [6]. The clinical effect of ITP depends on the degree of thrombocytopenia, on its response to therapy, and on bleeding. Our patient did not improve with first-line therapy, and splenectomy was excluded because of the risk of major bleeding, but an effective treatment was needed. Surgical or medical palliation was prevented by both thrombocytopenia and the lack of histological diagnosis.

Romiplostim is a second generation TRA which increases platelet count in a dose-dependent manner in ITP, also

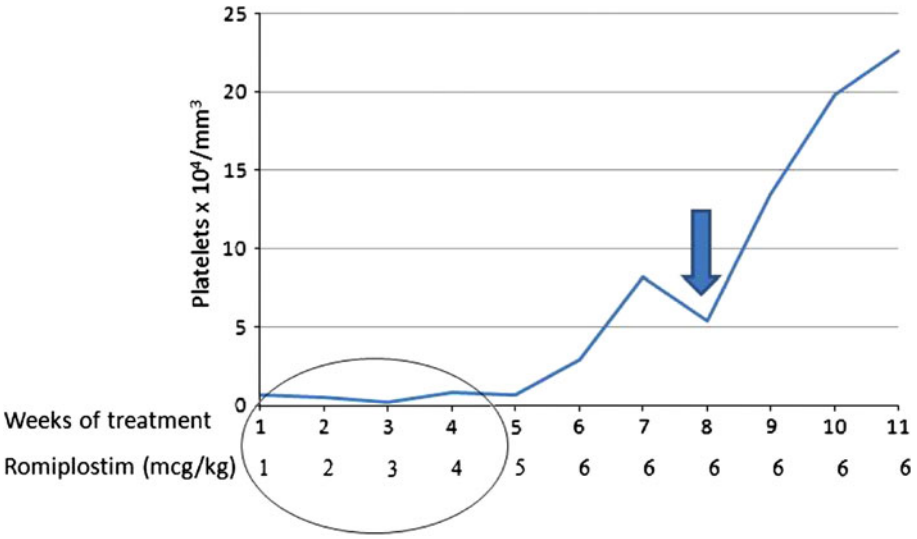

Fig. 1 Threshold effect of the dose of romiplostim on platelet count. No improvement was achieved with doses ≤4 μg/kg (*ellipse*). We also observed a transient drop in platelet count which is common during the early phases of treatment with romiplostim (*arrow*)

reducing the incidence and severity of bleeding. It is effective both in splenectomized and non-splenectomized subjects, with slight differences in time to response, median dosage, and duration of response between the two groups [7]. Unlike first-generation TRAs, it lacks sequence homology with endogenous thrombopoietin to avoid the formation of cross-reactive antibodies. Its efficacy relies on stimulation of the platelet production which is impaired in many ITP patients [8]. This approach is radically different from all the other treatments for ITP, the objective of which is to reduce the removal of platelets. Moreover, most lack approval for ITP by the Food and Drug Administration. Romiplostim is well-tolerated and the incidence short-term side effects (mainly headache and fatigue) were quite similar for romiplostim and placebo in clinical trials. Furthermore, exposure to romiplostim does not increase the rate of thrombotic events in primary ITP. Reversible increase in bone marrow reticulin and transitory rebound thrombocytopenia are the main side effects reported in ITP to date [9, 10]. Although licensed for chronic ITP, data about the efficacy and safety of romiplostim in patients with shorter duration of disease were available, as in the study of Kuter et al. [11], in which 36 % of patients had a history of ITP. Papers on the use of TRAs for patients with ITP secondary to hematological malignancies were also available [12–15]. Finally, it was the only feasible choice to increase platelet count, avoid bleeding, and enable both surgical palliation and histological diagnosis. Interestingly, time to platelets $>5 \times 10^4/mm^3$ was longer (7 vs. 2 weeks) and median dose was higher (6 vs. 2 μg/kg) than in non-splenectomized patients with primary ITP [7]. Furthermore, normally platelet count increases with romiplostim in a dose-dependent manner, but in our patient it suddenly increased from 5 μg/kg and became normal with 6 μg/kg, with an uncommon threshold-effect [16]. These observations suggest that secondary ITP might be less sensitive to romiplostim and, thus, might require higher doses. In our opinion this could be because of enhanced autoimmune activity induced by the neoplasm. Finally, potential risks of TRAs in cancer patients are thrombotic events (TEs), particularly when surgery is needed. The risk of TEs has been found to be increased in patients with chronic liver disease treated with the TRA eltrombopag, as in the ELEVATE study, in which 7 TEs of the portal venous system were recorded. However, the TEs observed in the ELEVATE study were considered to be unlikely to be relevant to the ITP patient population by the Committee for Medicinal Products for Human Use of the European Medicines Agency, because of the different pathophysiology of the two diseases and the different type and pattern of TEs observed [17]. Portomesenteric TEs have also been reported as a rare complication after abdominal surgery, mainly with laparoscopy and with procedures that involve the ligation of major portal tributaries [18]. Our patient underwent open surgery without ligation of major portal tributaries. Moreover, heparin prophylaxis restarted before the intervention. Although it seems unlikely that she underwent such a complication, TRAs must be used carefully before surgery.

To conclude, romiplostim was effective in refractory secondary ITP in a patient affected by serous ovarian carcinoma, with an uncommon threshold-effect of its dosage. TRAs might be useful in some circumstances, but their efficacy and safety in cancer patients must yet be defined. Thus, well-designed clinical trials are urgently needed to resolve this issue.

Conflict of interest Prof. Alberto Bosi received lecture fees from Amgen Inc. All other authors declare that they have no conflict of interest.

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