Life-threatening oxaliplatin-induced acute thrombocytopenia, hemolysis and bleeding: A case report

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To the Editor

Combination chemotherapy including the third generation platinum derivative oxaliplatin (l-OHP) represents a standard of care for colorectal cancer [1,2]. Recently, the combination of chemotherapeutic drugs with the novel molecular-targeted anti-VEGF monoclonal antibody, bevacizumab, has demonstrated to produce additive affects improving the patients' outcome [3]. Thus, regimens including l-OHP and bevacizumab are currently a standard treatment for metastatic colorectal cancer [4].

Common side effects of l-OHP are cumulative peripheral sensory neuropathy and delayed hematological toxicity, mainly due to myelosuppression. By contrast, bevacizumab does not induce any hematological toxicity, but increases the risk of hypertension, arterial thrombotic events, bleedings and gastrointestinal perforation [5].

We herewith report a case of a severe life-threatening thrombocytopenia, hemolysis and bleeding with acute onset during l-OHP and bevacizumab administration.

In December 2005 a 44-year-old woman was diagnosed of left colon cancer and synchronous multiple liver metastases. She underwent left hemicolectomy and subsequent anticancer therapy with 4 mg/kg bevacizumab on day 1; 85 mg/mq l-OHP on day 1; 400 mg/mq Fluorouracil (FU) on day 1 and 2; 200 mg/mq Folinic Acid on day 1 and 2; 1 200 mg/mq FU in 48-h continuous infusion on day 1 and 2. The schedule was repeated every 14 days. She reported a near complete response according to RECIST criteria and underwent the resection of liver metastases. The patient received 15 courses of therapy, 12 before and 3 after the liver surgery. The treatment was well tolerated during 14 courses, the patient reporting only occasional slight reduction in platelet counts (grade I–II WHO).

Before starting the 15th administration of therapy the patient had normal hematological values (Hb 13.9 g/dl; WBC 10 000/uL; N 68.5%; platelets 124 000/uL). One hour after bevacizumab administration and during the infusion of l-OHP, she developed chills, abdominal pain, nausea, purpura on the upper limbs and severe epistaxis. The blood test showed an acute reduction of platelet count (21 000/uL) and increased WBC count (19 900/uL). There were no signs of venus thromboembolic disease or consumption coagulopathy (PT 123%; INR 0.90; aPTT 38.5 sec and fibrinogen 327 mg/dl; D-dimers 70 mg/ml). She immediately received therapy with 8 mg desametasone i.v., 10 mg clorfenamina maleato i.v., 1 500 mg tranexanic acid in 30-min i.v. infusion and transfusion with platelets (2 units) which did not increase the platelet count. Epistaxis was blocked with local compression. Within few hours a diffusion of purpura to the whole body was observed. There were no signs of infections.

The next day blood tests were consistent with mild hemolysis [Hb 11.2 g/dl, direct antiglobulin test (DAT) positive], and platelet count was still low (10 000/μl). The platelet-reactive autoantibodies evaluated on platelet eluate were negative as well as the anti-cardiolipine, the anti-nucleus, the anti-DNA double strand and the anti-mitochondria antibodies. The creatinine, albumin, alanine aminotransferase, aspartate aminotransferase and total bilirubin levels were also within the normal range. During the next few days the patient received daily platelet transfusion and steroid therapy. Only after 5 days of therapy, the blood tests revealed normal platelet and hemoglobin counts (110 000/uL and 13.1 g/dl, respectively) and negative DAT. Interestingly, the blood test performed the day

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after chemotherapy showed an increase in IL10 and TNFα serum levels (28.6 pg/ml and 12.8 pg/ml, respectively) which resumed normality within 4 days.

l-OHP has been reported to induce very rarely life-threatening acute hematological toxicities with decrease of platelet counts [6], in some cases associated with hemolyisis [7–9] and, occasionally, with neutropenia [10]. In some cases acute hemolytic anaemia was the only hematologic toxicity [11–14]. As observed in our patient and others who reported similar clinical pictures, the acute toxicity occurred after several administration of l-OHP suggesting an immuno-mediated mechanism, boosted by repeated drug exposure. However, two independent pathogenetic mechanisms have been proposed for this toxicity. Some authors described the formation of autoantibodies to erythrocytes and, more rarely, to platelets and neutrophils as a result of l-OHP adsorption on blood cells [6,7,10,12,14], suggesting that the mechanism for this adverse event should be a peripheral immuno-mediated blood cells disruption which resembles the Evans' syndrome [13]. By contrast, other authors reported high levels of cytokines (i.e. IL6, IL10 and TNFα) suggesting that this l-OHP-dependent toxicity may be triggered by a massive release of pro-inflammatory molecules [8,15]. Interestingly, in this perspective Tonini et al., described a cytokine-release syndrome with chills, high fever, hypotension, abdominal pain, nausea, often diarrhea, but no signs of thrombocytopenia or hemolysis in patients treated with long-term l-OHP-containing chemotherapy [16]. In our case we observed that both mechanisms are likely to be involved since laboratory tests exhibited either signs of increased productions of IL10 and TNFα or positive DAT. The negative test for platelet-bound antibodies does not exclude the hypothesis that the platelet disruption may be antibody-mediated, since this test is quite frequently false negative. Thus, the release of cytokines may be responsible for the inflammatory-like systemic symptoms, whereas the immuno-mediated mechanism may account for blood cells reduction, and the full development of the toxicity may require the activation of both mechanisms, explaining why in some cases a partial clinical picture has been described. Therefore, steroid therapy before and after l-OHP therapy could be valuable to attenuate the risk and the severity of this adverse event. Indeed, hypersensitivity reactions to l-OHP may be prevented by continuous infusional schedules [17] or desensitization pharmacological protocols [18].

Finally, this is, to our knowledge, the first case of acute thrombocytopenia, hemolysis and bleeding in a patient treated with combination therapy containing either l-OHP or bevacizumab. Indeed, laboratory examination did not reveal any sign of platelet consumption suggesting that thromboembolic events are not involved in this acute toxicity and bevacizumab is not its major cause. Furthermore, thrombocytopenia is *per se* a potential cause of bleeding and a gastrointestinal bleeding has been already described in a patient who reported an acute drop of platelet count during l-OHP therapy [8]. However, oncologists need to be aware of the risk of severe bleedings in patients with this rare but potentially life-threatening l-OHP-dependent hematologic toxicity following the concomitant administration of bevacizumab.

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Chronic myelogenous leukemia exhibiting trisomy 14 due to a Robertsonian translocation with philadelphia chromosome

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To the Editor

Chronic myelogenous leukemia (CML) is a genetically heterogenous disease that is frequently associated with cytogenetic abnormalities [1]. A second philadelphia (Ph) chromosome, trisomy 8, isochromosome 17q and trisomy 19 are the most common karyotypic abnormalities found in CML patients [2]. Trisomy 14 is a rare chromosomal aberration that is usually observed in myelodysplastic syndrome, myeloproliferative disorders, atypical chronic myeloid leukemia and acute myeloid leukemia which is associated with old age, thrombocytosis and poor prognosis [3–6]. Robertsonian translocations are rarely reported in hematological malignancies and the incidence is estimated to be 1/10.000 [7]. However, trisomies resulted from robertsonian translocations are extremely rare [8]. In the literature there is only one CML patient diagnosed in blastic phase carrying both Ph chromosome and translocation (14;14) who has a similar disease progress as in our case [9].

A 55-year-old man was admitted to our hospital with fatigue, weakness, weight loss, night sweating, abdominal pain, dry cough and fever of more than 39°C for 10 days. On physical examination, there was echymosis along the skin of the extremities, hepatomegaly and massive splenomegaly. The complete blood count showed white blood cells (WBC) 213×10^9/L, hemoglobin (Hb) 8.1 g/dl, hematocrit (Hct) 27.6% and platelets (PLT) 137×10^9/L. Biochemical parameters were within normal limits except lactate dehydrogenase (LDH) 1794 U/L. Peripheral blood smear (PS) revealed the leukocytosis and the presence of 60% of myeloloblastic cells where 3% of them were peroxidase positive. Bone marrow aspiration and biopsy specimen were consistent with the diagnosis of acute myeloblastic leukemia FAB myelomonocytic type (AML-FAB4) showing 60% of myelomonoblastic infiltration with CD34+, MPO+, Lyzozyme+, CD68+ and CD3−, CD79a−, TdT- by immunohistochemical staining. Broad spectrum antibiotherapy was started for the febrile status and cytarabine and idarubicine were given as a remission induction chemotherapy. One month after the chemotherapy, his hematological parameters improved to WBC: 3.1×10^9/L where 65% of them were neutrophils, Hb: 9.4 g/dl, Hct: 29.8%, PLT: 370×10^9/L. However, bone marrow aspiration showed 50% myeloblastic cell infiltration. After the salvage therapy with fludarabine plus cytarabine, a hematological remission was not achieved. At diagnosis, the karyotype obtained from unstimulated culture of bone marrow showed trisomy 14 due to Robertsonian translocation, a philadelphia chromosome and was reported as 46,XY,t(14;14)(q10;q10),t(9;22) (q34;

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