Thrombocytopenia due to low-dose colchicine therapy: A possible drug interaction with nivolumab and implications for supportive care

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To the Editor,

Hyperuricemia and gout often accompany hematologic and oncologic disorders. Colchicine, long used to manage gout, is rarely associated with hematologic toxicity. Infrequently, pancytopenia accompanied by gastrointestinal abnormalities may follow high dose or intravenous colchicine administration in subjects with underlying renal or hepatic dysfunction [1–3]. A case of thrombocytopenia during low-dose colchicine administration for gout prophylaxis is now described and a drug interaction with the investigational PD-1 pathway inhibitor, nivolumab is suggested [4].

Case report

A 70-year-old male was diagnosed with malignant melanoma metastatic to brain, lung, rib, liver, mesentery and small intestine in February 2013. He received gamma knife treatment of brain metastases on two occasions; a five-day course of IL-2 during April 2013 (without a tumor response); and a single intravenous dose of ipilimumab (3 mg/kg) combined with nivolumab (1 mg/kg) on 7 June 2013. He then developed diarrhea; C. difficile colitis; small bowel obstruction with gastrointestinal bleeding (requiring ileal resection on 31 July 2013); and asymptomatic portal and left common iliac vein thromboses on 26 August 2013 (treated with 1.5 mg/kg/day of enoxaparin subcutaneously).

Intravenous nivolumab (3 mg/kg) every two weeks was begun on 29 August 2013. The first dose was followed by seven days of fever (temperatures between 37.9°C and 39.2°C). Eleven days after beginning nivolumab, podagra developed and oral colchicine therapy was begun at a dose of 1.8 mg per day with rapid improvement. The serum uric acid level was 7.6 mg/dl two days after the onset of symptoms (normal range = 3.5–7.0 mg/dl) but had been 5.9 mg/dl seven weeks previously. Colchicine was discontinued after three days but podagra recurred 13 days later. Colchicine was reinstituted for one month. However, acute bilateral knee pain and swelling developed six days after colchicine was discontinued. The serum uric acid level had increased to 8.6 mg/dl and remained > 7.5 mg/dl thereafter. Joint symptoms again rapidly resolved with the reinstitution of colchicine, which was then continued for 12 weeks. The platelet count was 160 000/mm³ (normal range = 150 000–350 000/mm³) when the third course of colchicine was instituted but fell to 125 000/mm³ eight weeks later and reached a nadir of 115 000 mm³ after 12 weeks (Figure 1a). The absolute neutrophil count (ANC) also decreased during this time to a nadir of 2200/mm³ (Figure 1b) but hemoglobin values ranged from 13.9 g/dl to 14.8 g/dl. Serum BUN, creatinine, alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphate and gamma glutamyl transferase values were all normal. By six weeks after colchicine was discontinued, the platelet count returned to normal and the ANC increased to 3200/mm³. Platelet counts remained between 132 000/mm³ and 151 000/mm³ during an additional nine months of follow-up on continued nivolumab therapy with all but three of 19 values ≥ 145 000/mm³ while the ANC remained = 3200/mm³. Biweekly nivolumab was continued throughout the course and daily enoxaparin was continued until six weeks after colchicine was discontinued. The patient never experienced nausea, vomiting or diarrhea. Platelet counts on four occasions during the year prior to the development of metastatic disease were 139 000/mm³ to 175 000/mm³ (mean = 159 000/mm³).

Discussion

In this subject, treatment with colchicine was instituted for recurrent episodes of gout since both non-steroidal anti-inflammatory agents and steroids were contraindicated by ongoing treatment with enoxaparin and nivolumab, respectively, and since concerns about drug interactions precluded the use of allopurinol [5].

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Thrombocytopenia developed eight weeks after beginning the third course of colchicine (Figure 1a) and resolved 4–6 weeks after colchicine was discontinued. More profound thrombocytopenia may have occurred had not blood counts been obtained every two weeks on the investigational protocol. The ANC also decreased during colchicine therapy but did not reach neutropenic levels (Figure 1b). This time course suggests that thrombocytopenia was due to non-immune marrow damage, a finding consistent with previous reports [1,2]. Neither enoxaparin nor nivolumab alone are likely responsible for the fall in the platelet count or ANC since recovery occurred despite continued use of both these agents.

Although hematologic toxicity due to colchicine has been noted with high doses given intravenously to subjects with renal or hepatic dysfunction [1,2], no cases of hematoxicity occurred in two studies of the long-term (>2 year) use of low-dose colchicine (1–1.8 mg/day) in a total of 293 patients for the prophylaxis of either gout or familial Mediterranean fever [1,2,5,6]. It is of note then, that colchicine metabolism involves both CYP3A4 and P-glycoprotein and that interactions between colchicine and other drugs metabolized by these pathways have been described [3,7]. Although metabolism of nivolumab is undefined, other monoclonal antibodies (i.e. rituximab and cetuximab) block P-glycoprotein activity [8,9]. Moreover, nivolumab and other PD-1 antagonists may impair CYP-mediated metabolism [10]. Thus, a drug interaction between colchicine and nivolumab can explain the thrombocytopenia observed in this subject. Since enoxaparin does not interact with either P-glycoprotein or the CYP450 system, it is unlikely that thrombocytopenia resulted from an interaction of colchicine and enoxaparin [11].

Many antineoplastic drugs and symptom-directed medications also interact with CYP3A4 and P-glycoprotein (see Supplementary Table I, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.1002572) [12–18] and the metabolism of other agents in both these categories remain undefined. Thus, similar interactions may not be infrequent in oncologic settings. However, while the possibility of drug-drug interactions involving supportive care medications in oncology patients has been suggested [18], there are no previous reports of hematologic toxicity resulting from the concurrent use of anti-neoplastic and symptom-directed medications. Thus, these interactions may go unrecognized with cytopenias attributed solely to the chemotherapeutic agents, leading to erroneous dose reduction or discontinuation of anti-neoplastic treatments. This possibility is of particular importance with the earlier implementation of palliative care approaches in the setting of advanced malignancies [19].

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Supplementary material available online

Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.1002572).