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 ipilumab (3 mg/kg) combined with nivolumab (1 mg/kg) on 7 June 2013. He then developed diarrhea; C. dificile 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/mm^3 (normal range = 150 000–350 000/mm^3) when the third course of colchicine was instituted but fell to 125 000/mm^3 eight weeks later and reached a nadir of 115 000 mm^3 after 12 weeks (Figure 1a). The absolute neutrophil count (ANC) also decreased during this time to a nadir of 2200/mm^3 (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/mm^3. Platelet counts remained between 132 000/mm^3 and 151 000/mm^3 during an additional nine months of follow-up on continued nivolumb therapy with all but three of 19 values $\geq$ 145 000/mm^3 while the ANC remained $\geq$ 3200/ mm^3. 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/ mm^3 to 175 000/mm^3 (mean = 159 000/ mm^3).

Discussion

In this subject, treatment with colchicine was instituted for recurrent episodes of gout since both nonsteroidal 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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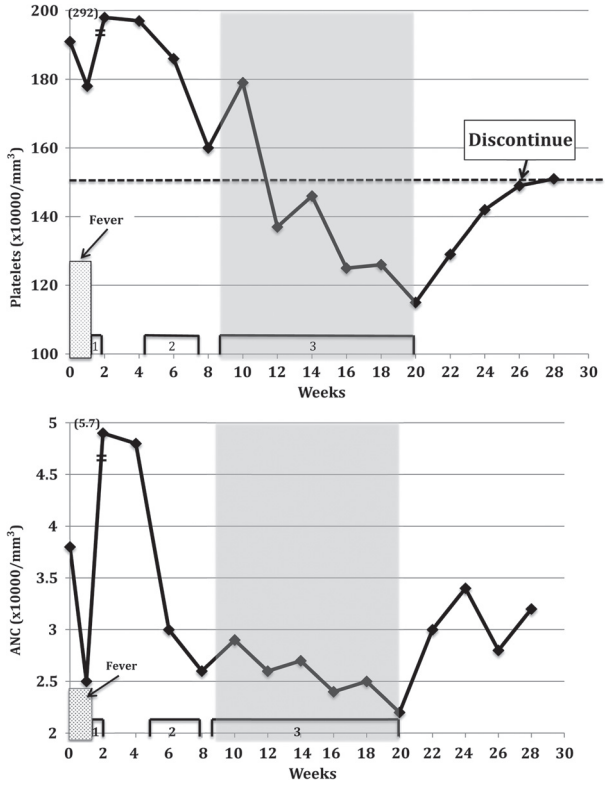

Figure 1. Platelet and neutrophil counts related to oral colchicine therapy. Dashed line indicates lower normal platelet count level of 150 000/mm^3. Numbered boxes on x-axis indicate courses of oral colchicine therapy as follows: 1.8 mg/day for 3 days, 1.8 mg/day for 3 days; then 1.2 mg/day for 11 days; then 0.6 mg/day for 14 days, 1.8 mg/day for 1 day; then 1.2 mg/day for 7 days; then 0.6 mg/day for 65 days, ANC, absolute neutrophil count.

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 hematotoxicity 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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References

[1] Levy M, Spino M, Reid SE. Colchicine: A state of the art review. Pharmacotherapy 1991;11:196–211.
[2] Bonnel RA, Villaboa ML. Karwolski CB, Beitz J. Deaths associated with inappropriate intravenous colchicine administration. J Emerg Med 2002;22:385–7.
[3] Terkeltraub RA. Colchicine update 2008. Semin Arthritis Rheum 2009;38:411–9.
[4] Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, et al. Survival, durable tumor remission and long-term safety in patients with advanced melanoma treated with nivolumab. J Clin Oncol 2014;32:1020–30.
[5] Yu TF, Gutman AB. Efficacy of colchicine prophylaxis in gout. Ann Int Med 1961;55:179–92.
[6] Peters RS, Lehman TJ, Schwabe AD. Colchicine use for familial Mediterranean fever. West J Med 1983;138:43–6.

[7] Ben-Chetrit E, Levy M. Colchicine: 1998 update. Semin Arthritis Rheum 1998;28:48–59.
[8] Paule B, Castagne V, Picard V, Saffroy R, Adma R, Guettier C, et al. MDR1 Polymorphism role in patients treated with cetuximab and irinotecan in irinotecan refactory colorectal cancer. Med Oncol 2010;27:1066–72.
[9] Ghetie M-A, Crank M, Kufert S, Pop I, Vitetta E. Rituximab but not other anti-CD20 antibodies reverses multidrug resistance in 2 B lymphoma cell lines, blocks the activity of P-glycoprotein (P-gp) and induces P-gp to translocate out of lipid rafts. J Immunother 2006;29:536–44.
[10] Harvey RD, Morgan ET. Cancer, inflammation, and therapy: Effects on cytochrome P450-mediated drug metabolism and implications for novel immunotherapeutic agents. Clin Pharmacol Therap 2014;96:449–57.
[11] Stolling DP, Jaehde U, Wiese M, Bendas G. Are low molecular weight heparins able to sensitize chemoresistant tumor cells? Int J Clin Pharmacol Therap 2013;51:70–3.
[12] Marzolini C, Paus E, Buclin T, Kim RB. Polymorphisms in human MDR1 (P-glycoprotein): Recent advances and clinical relevance. Clin Pharmacol Ther 2004;75:13–33.
[13] Teft WA, Mansell SE, Kim RB. Endoxifen, the active metabolite of tamoxifen, is a substrate of the efflux transporter, P-glycoprotein (multidrug resistance 1). Drug Metab Disposition 2011;39:558–62.
[14] Deenen MJ, Cats A, Beijnen JH, Schellens JHM. Part 2: Pharmacogenetic variability in drug transport and phase 1 anticancer drug metabolism. Oncologist 2011;16:820–34.
[15] Zrieki A, Farinotti R, Buyse M. Cycoloxygenase inhibitors down regulate P-glycoprotein in human colorectal Caco-2 cell line. Pharm Res 2008;25:1991–2001.
[16] Manov I, Bashenko Y, Hirsh M, Iancu TC. Involvement of multidrug resistance P-glycoprotein in acetaminophen-induced toxicity in hepatoma-derived HepG2 and Hep3B cells. Basic Clin Pharmacol Toxicol 2006;99:213–24.
[17] Wang J-S, Zhu H-J, Markowitz JS, Donovan JL, DeVane CL. Evaluation of antipsychotic drugs as inhibitors of multidrug resistance transporter P-glycoprotein. Psychopharmacol 2006;187:415–23.
[18] Blower P, de Wit R, Goodin S, Aapro M. Drug-drug interactions in oncology: Why are they important and can they be minimized? Crit Rev Oncol/Hematol 2005;55:117–42.
[19] Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small cell lung cancer. New Engl J Med 2010; 363:733–42.

Supplementary material available online

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