Published in final edited form as:

Inflamm Bowel Dis. 2010 September ; 16(9): 1454–1456. doi:10.1002/ibd.21205.

Treatment Associated Acute Myeloid Leukemia in a Patient with Crohn's Disease on 6-MP

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To the Editors

Immunomodulatory therapies such as 6-Mercaptopurine (6-MP) and Azathioprine provide high remission rates and success in avoiding steroid dependence in patients with Inflammatory Bowel Disease (IBD). However, these treatments are not without adverse effects including leucopenia, liver function test abnormalities, infection, headache, pancreatitis, fever, hair loss, rash as well as more alarming side effects including malignancy.¹ IBD patients treated with 6-MP are estimated to have a 4 fold increased risk of developing lymphoma in comparison to the general population, a complication which may be associated with anti-tumor necrosis factor therapy as well.² In addition to lymphoma, 6-MP therapy has also been associated with more rare treatment associated acute hematopoietic malignancies. This case report illustrates the clinical challenges in diagnosing the rare and ultimately fatal side effect of 6-MP treatment associated acute myeloid leukemia in a patient with Crohn's Disease.

A 62-year-old woman with a 20-year history of ileal and right colonic Crohn's Disease (CD) was recently referred to this hospital with a complaint of frequent bruising. In 2002, the patient developed perianal fistulas and her gastroenterologist initiated therapy with 6-MP. In 2006, the patient developed severe stricturing disease requiring an ileo-right-hemicolectomy with ileotransverse anastomosis complicated by chronic vitamin B12 deficiency and macrocytic anemia. Postoperatively, the patient was maintained on 100 mg of 6-MP daily and 2g of mesalamine daily. Although thiopurine methyltransferase (TPMT) genetic testing was normal, her primary gastroenterologist had difficulty maintaining the patient's 6-thioguanine (6-TGN) levels without developing elevated levels of toxic 6-methylmercaptopurine metabolites. Thus, in March 2008, 100 mg of allopurinol daily was added to her regimen, which achieved a remarkable decrease in the amount of 6-MP needed for therapeutic levels of 6-TGN (25mg of 6-MP twice weekly). Relevant pharmacologic monitoring and routine blood tests are displayed in Table 1.

The patient's past medical history is also notable for psoriasis complicated by psoriatic arthritis. Her dermatologist started her on methotrexate and infliximab, but ultimately maintained her on etanercept. However, this was discontinued in July 2008 due to the patient's ongoing leucopenia.

In April 2009, the patient first noticed easy bruising but did not experience mucosal bleeding, petechiae, fatigue, fever or night sweats. She lost 40 lbs over the past year

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FINANCIAL DISCLOSURES: There are no conflicts of interest to disclose.

intentionally by dieting and exercise. She was referred to a hematologist for evaluation and a peripheral smear demonstrated 23% circulating blasts (Figure 1A). A bone marrow biopsy demonstrated 50% marrow cellularity, markedly decreased maturing myeloid elements, and megakaryocytes, all consistent with *Acute Myeloid Leukemia* (AML) (Figure 1B). A cytometric analysis was notable for 15% myeloid blasts (CD33+, CD13+, CD117+, CD34+, HLA-DR+, CD64-/-, CD11c+). Karyotype analysis demonstrated 20 metaphases with monosomy 7 as the sole aberration (Figure 1C). The patient was admitted and an induction with a chemotherapy regimen of bortezomib, daunorubicin, and cytarabine was initiated.

Treatment related acute myeloid leukemia and myelodysplastic syndrome is a well characterized, rare, and incompletely understood phenomenon. Patients are typically exposed to cytotoxic therapies such as topoisomerase II inhibitors or alkylating agents such as 6-MP and go on to develop mutational events leading to fatal leukemic disease. This serious complication appears to be idiosyncratic and unrelated to the dose and duration of exposure to the agent, however some associations with low TPMT activity and elevated 6-TGN levels have been made.³ Classically, karyotype analysis demonstrates the loss of part or all of chromosomes 5 and/or 7 in more than 90% of patients.⁴ Although not standardized, treatment generally consists of anthracyclines and cytarabine with possibly bone marrow transplant.⁴ Median survival is 7-9 months.⁴

There has been an increased incidence of AML and MDS⁵ noted overall in patients with ulcerative colitis⁶ and CD^{7, 8} even in the pre-immunomodulatory era, suggesting an association between inflammatory bowel disease (IBD) itself and these hematopoietic malignancies. However, there have been few reports of 6-MP treatment associated AML in IBD with classically associated cytogenic abnormalities as we demonstrate here.⁹ Our patient developed AML despite regular monitoring, highlighting the difficulty of balancing the expected leucopenia commonly seen with 6-MP treatment and anemia commonly seen in IBD, with the subtle changes that suggest the development of a malignancy. Furthermore, the use of allopurinol to boost 6-TGN levels as well as the concomitant exposure to anti-TNF agents in this patient may support the notion that increasing levels of multimodal immunomodulating therapies may be especially associated with malignancy.

Acknowledgments

GRANT SUPPORT: None

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Abbreviations

CD	Crohn's Disease
IBD	Inflammatory Bowel Disease
AML	Acute Myeloid Leukemia
6-MP	6-Mercaptopurine
6-TGN	6-Thioguanine Nucleotides
6-MMP	6-Methylmercaptopurine
TPMT	Thiopurine Methyltransferase

FIGURE 1.

(A) Peripheral smear demonstrating 23% circulating blasts. (B) Bone marrow biopsy with 50% marrow cellularity, markedly decreased maturing myeloid elements, and megakaryocytes, all consistent with the diagnosis of AML. (C) Karyotype analysis demonstrating 20 metaphases with monosomy 7 as the sole aberration, classically found in 90% of treatment-associated cases of AML.⁴

TABLE 1
6-Mercaptopurine Dosing, Metabolite Levels, Blood Counts, and Routine Monitoring

Date	Allopurinol	6MP	6TGN pmol/8×10 ⁸ RBC	6MMP pmol/8×10 ⁸ RBC	WBC ×1000/uL	ANC	HCT %	MCV uM ³	PLT ml/uL	AST/ALT U/L	Tbili mg/dL
Apr-07	---	100mg qd	319	4220	5.9		34	108	308		
Jan-08	---	125mg qd	150	9353						63/78	1.6
Mar-08	100mg qd	25mg qd	476		3.4		33				
Mar-08	100mg qd	25mg qod	515		3.8		32	111			
Apr-08	100mg qd	25mg q3d	158	<Assay	4.9		34	114	278	60/54	
May-08	100mg qd	25mg tiw	218	<Assay	5.5		32	111	238	85/62	
Jul-08	100mg qd	25mg q3d	312	<Assay	2.5		33				
Jul-08	100mg qd	25mg biw	317	<Assay	2.5	1200	33	104	170 (Clumps & Large Pits)	50/45	1.4
Aug-08	100mg qd	25mg biw	251	<Assay	2.8		32	104	Count (Clumped)	58/56	1.5
Sep-08	100mg qd	25mg biw	305	<Assay	1.9		31	104	Count (Clumped)	72/57	1.6
Nov-08	100mg qd	25mg qwk									
Dec-08	100mg qd	25mg biw	151	<Assay	2		33	105			
Jan-08	100mg qd	25mg biw	118	<Assay	2.6		34	106	Count (Clumped)		
Mar-09	100mg qd	25mg biw	257	<Assay	5.2		32	107	Count (Clumped)	51/35	1.4
Apr-09	100mg qd	25mg biw			3.3	1400	32	107	Count (Clumped)	38/39	1
Apr-09	125mg qd	25mg biw									
May-09	125mg qd	----			3.5	1300	33	106	99		
Jun-09	----	----			2.9	600	35	105	Count (Clumped)		
Jul-09	----	----			1.9	170	32.8	101	81		