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ACUTE MYELOID LEUKEMIA IN A PATIENT RECEIVING PHASE III CLINICAL TRIAL OF TOFACITINIB (XELJANZ) THERAPY FOR ULCERATIVE COLITIS: A CASE STUDY WITH LITERATURE REVIEW

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A B S T R A C T

A 53 year old male with ulcerative colitis (UC) in phase III clinical trial of Tofacitinib therapy for 2 years was admitted for pancytopenia and circulating blasts in peripheral blood. Subsequent bone marrow biopsy demonstrated diffuse leukemic infiltrate with nearly absent normal hematopoiesis. Leukemic cells showed minimal morphological differentiation. Flow cytometry study revealed acute myeloid leukemia (AML), with co-expression of CD5 (dim), CD7 (heterogeneous) and CD10 (h). The leukemic cells were negative for intracellular myeloperoxidase(MPO), CD3, Tdt and CD79a, which were confirmed by immunohistochemical studies. AML cells showed a complex karyotype 41-43, -1,dup(1)(p32p36.3),add(4)(q22),del(5)(q31q35),add(7)(q36),+8,add(8)(q24),-13,add(14)(p10),-15,-17,+19,-22[cp20]. FISH study was negative for RPN1, MECOM, RUNX1T1, MLL, PML, CBF-beta, RARA, and RUNX1 gene mutations. Patient showed no response to cytarabine based "7+3" chemotherapy regimen, with persistent AML in the bone marrow biopsy on day 14 post introduction chemotherapy. Unresponsive to further treatment, the patient died 23 days after the initial AML diagnosis due to multiple complications including metabolic encephalopathy, neutropenic fever, sepsis, acute kidney injury and acute diarrhea. This is the first case report on the clinicopathological features of AML in patients receiving Tofacitinib therapy for UC in a phase III clinical trial. Further clinical studies are needed for the evaluation of long term safety of Tofacitinib therapy in these patients.

INTRODUCTION

Tofacitinib (Xeljanz) is a Janus kinase (JAK) inhibitor and recently approved by FDA for the treatment of rheumatoid arthritis (RA) in adults who have had an inadequate response to, or are intolerant of, methotrexate [1]. It targets the intracellular signaling pathways in the inflammatory cytokine network, and directly inhibits signaling in an important subset of pro-inflammatory cytokines including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 [2, 3]. The efficacy and safety of Tofacitinib have been studied in a variety of patient populations with moderate-to-severe active RA in multiple clinical trials [4,5,6,7]. The association between Tofacitinib treatment and the incidence of malignancy (lung cancer, breast cancer, gastric cancer and lymphoma) in RA patients has been previously studied [8]. There has been no acute myeloid leukemia reported in patients who take Tofacitinib yet. This study reveals the clinicopathological features of acute myeloid leukemia developed in a patient receiving phase III clinical trial of Tofacitinib therapy for ulcerative colitis.

Case Report

Patient information and clinical presentation

The patient was a 53 year old male with ulcerative colitis and had being on a phase III clinical trial with Tofacitinib therapy for about 2 years. The patient was found to have pancytopenia and Tofacitinib was stopped. After seeing his primary care physician, the patient was admitted to the hospital for further evaluation. At admission he presented with multiple medical conditions including neutropenic fever, elevated liver function tests, skin rash and pancytopenia. A peripheral blood smear review was performed and many circulating blasts were identified. A

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bone marrow biopsy was performed for the evaluation of acute leukemia.

Pathological studies of the initial bone marrow biopsy

Histological examinations: Routine histological examination of the bone marrow core biopsy showed diffuse blastic infiltrate with nearly absent normal hematopoiesis (Figure 1). Numerous blasts were present on the bone marrow aspirate (>80%) and peripheral blood smears. The blasts showed minimal morphological differentiation.

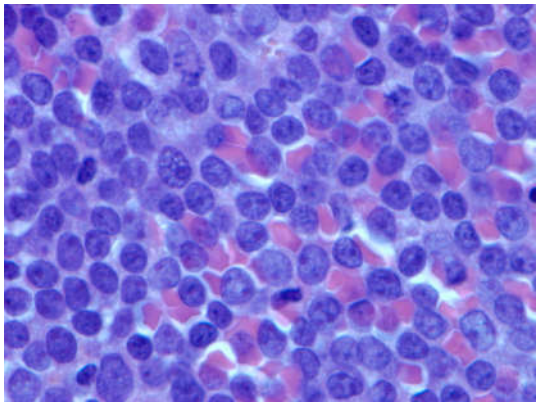

Figure 1 Bone marrow core biopsy showed diffuse blastic infiltrate and nearly absent normal hematopoiesis.

Flow cytometry results*:* Multicolor flow cytometry evaluation reported approximately 86% blasts with myeloid immunophenotype: positive for CD5 (dim), CD7 (heterogeneous, h), CD10 (h), CD11b (dim), CD13, CD33, CD34, CD38 (heterogeneous), CD45 (dim), CD71, CD117 and HLA-DR. The blasts were negative for additional myeloid markers (CD14, CD15, CD16, CD36, CD41, CD64), T-cell markers (CD2, CD3, CD4, CD8), additional B-cell markers (CD19, CD20, kappa, lambda, intracellular Tdt) and the NK cell marker CD56. Flow cytometry study on peripheral blood showed that the blasts were negative for intracellular MPO, CD3 and CD79a.

Cytogenetic and FISH results: Cytogenetic analysis revealed a complex hypodiploid karyotype with 41-43 chromosomes (Figure 2).

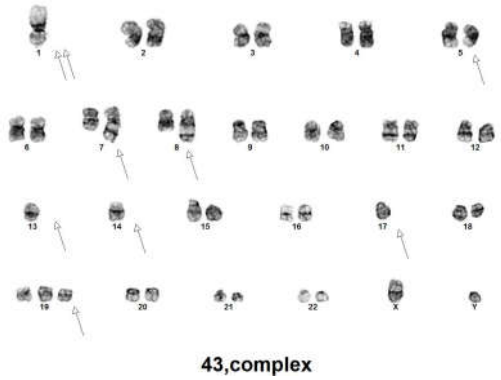

Figure 2 Cytogenetic analysis of AML cells revealed a complex hypodiploid karyotype with 41-43 chromosomes.

The composite karyotype included: 1) loss of chromosomes 1, 13, 15, 17, and 22; 2) duplication of chromosome 1p; 3) additional material of unknown origin attached at chromosome bands 4q22, 7q36, 8q24, and 14p10; 4) deletion of chromosome 5q; 5) gain of chromosomes 8 and 19; and 6) one marker chromosome. Fluorescence in situ hybridization (FISH) was performed utilizing an AML panel and was negative for RPN1, MECOM, RUNX1T1, MLL, PML, CBF-beta, RARA, and RUNX1 gene mutations.

PCR studies for NPM1, FLT3 and CEBPA gene mutations: Molecular tests were negative for NPM1, FLT3 and CEBPA gene mutations in the acute leukemic cells.

Pathological studies of the bone marrow biopsy at day 14 post introduction chemotherapy

Repeat bone marrow biopsy was performed at day 14 post introduction chemotherapy. Patient showed no response to chemotherapy received and bone marrow biopsy examination demonstrated prominent persistent acute myeloid leukemia. The leukemic cells showed same morphological, immunophenotypic and cytogenetic features as those at the initial diagnosis.

Clinical management, chemotherapy and clinical course

After the initial diagnosis of acute myeloid leukemia, the patient received "7+3" chemotherapy regimen with cytarabine and daunorubicin plus supportive treatments including transfusion of blood products. Patient showed no improvement and the clinical course was complicated with metabolic encephalopathy, sepsis, acute kidney injury, acute diarrhea, and severe pancytopenia due to both AML and chemotherapy. Without response to further treatment, the patient died at day 23 post the initial diagnosis of AML due to multiple complications.

DISCUSSION

In addition to RA, Tofacitinib has being investigated in clinical trials for other inflammatory diseases and demonstrated a significant dose-dependent improvement in clinical presentation and clinical remission in patients with moderately-to-severely active ulcerative colitis [9,10]. However, as an immunosuppressant, Tofacitinib therapy posts the patients with increased risk for secondary infections and possible malignancy [11,12]. In this study, the patient with uncomplicated ulcerative colitis developed acute myeloid leukemia after 2 years of Tofacitinib therapy. The acute leukemic cells showed complex hypodiploid karyotype and were resistant to the standard chemotherapy. The patient experienced multiple complications including metabolic encephalopathy, acute kidney injury, sepsis and neutropenic fever with an aggressive clinical course.

Therapy-related AML (t-AML) is a well-recognized complication after exposure to chemotherapy, radiotherapy, or immunosuppressive therapies in patients with primary malignant or non-malignant disorders [13]. Autoimmune diseases are the most common non-malignant conditions associated with t-AML in these patients [14, 15]. Although unclear, the possible explanation includes a common genetic predisposition, the effects of treatments for autoimmune diseases and direct damage of the bone marrow cells by autoimmune conditions [16, 17]. Ulcerative colitis was associated with

an increased risk of AML in some studies [18]. However, other studies have reported no such relation between ulcerative colitis and the risk of AML [19,20, 21].

Multiple studies have been published on the safety of Tofacitinib therapy in RA patients and shown no significant increase in the rate of lung cancer, gastric cancer, skin cancer and lymphoma when compared with the population based data [22]. However, systemic analysis is still lacking for Tofacinitib treatment in patients with ulcerative colitis. Questions remain about the safety of this medicine with potential risk for secondary malignancy and its use has not been approved for the treatment of rheumatoid arthritis by the European Medicines Agency [12], although the second review by the same agency is currently undertaken. More clinical studies with long term follow up may be needed to further answer the questions before this medicine become a standard therapy for patients with RA and ulcerative colitis.

References

1. Kremer JM, Bloom BJ, Breedveld FC, *et al*. The safety and efficacy of a JAK inhibitorin patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. Arthritis Rheum 2009; 60:1895–905.
2. Flanagan ME, Blumenkopf TA, Brissette WH, Brown MF, Casavant JM, Shang-Poa C, *et al*. Discovery of CP-690,550: a potent and selective Janus kinase (JAK) inhibitor for the treatment of autoimmune diseases and organ transplant rejection. *J Med Chem*. 2010; 53:8468–84.
3. Ghoreschi K, Jesson MI, Li X, Lee JL, Ghosh S, Alsup JW, *et al*. Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). *J Immunol.* 2011; 186:4234–43.
4. Wollenhaupt J, Silverfield J, Lee EB, *et al*. Safety and efficacy of tofacitinib, an oral Janus kinase inhibitor, for the treatment of rheumatoid arthritis in open-label, longterm extension studies. *J Rheumatol* 2014; 41:837–52.
5. Lee EB, Fleischmann R, Hall S, *et al*. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med 2014; 370:2377–86.
6. Fleischmann R, Kremer J, Cush J, *et al*. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med* 2012; 367:495–507.
7. van der Heijde D, Tanaka Y, Fleischmann R, *et al*. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum 2013; 65:559–70.
8. Scott, L.J. Tofacitinib: A Review of its Use in Adult Patients with Rheumatoid Arthritis. Drugs (2013) 73: 857
9. Panés J, Chinyu Su C, Bushmakin AG, Cappelleri JC, Mamolo C and Healey P. Randomized trial of tofacitinib in active ulcerative colitis: analysis of efficacy based on patient-reported outcomes. BMC Gastroenterology2015; 15:14
10. Sandborn WJ, Ghosh S, Panes J, Vranic I, Su C, Rousell S, *et al*. Study A3921063 Investigators: Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med*. 2012;367:616–24.
11. Wojciechowski D, Vincenti F. Tofacitinib in kidney transplantation. Expert OpinInvestig Drugs. 2013;22(9):1193-9
12. Troy Brown. EU Declines to Approve Tofacitinib (Xeljanz) for RA. Medscape Medical News. July 26, 2013
13. Leone G, Mele L, Pulsoni A, Equitani F and Pagano L. The incidence of secondary leukemias. Haematologica 1999; 84:937-945
14. Mir Madjlessi SH, Farmer RG, Weick JK. Inflammatory bowel disease and leukemia.A report of seven cases of leukemia in ulcerative colitis and Crohn's disease and review of the literature. Dig Dis Sci. 1986;31(10):1025-31.
15. Ramadan SM, Fouad TM, Summa V, Hasan SKH, and Lo-Coco F. Acute myeloid leukemia developing in patients with autoimmune diseases. Haematologica. 2012 Jun; 97(6): 805–817
16. Askling J, Fored CM, Baecklund E, Brandt L, Backlin C, Ekbom A, Sundstrom C, Bertilsson L, Coster L, Geborek P, Jacobsson LT, Lindblad S, Lysholm J, Rantapaa-Dahlqvist S, Saxne T, Klareskog L, Feltelius N. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis 2005;64:1414–1420
17. Anderson LA, Pfeiffer RM, Landgren O, Gadalla S, Berndt SI and Engels EA. Risks of myeloid malignancies in patients with autoimmune conditions. *British Journal of Cancer* 2009;100:822–828
18. Askling J, Brandt L, Lapidus A, Karlen P, Bjorkholm M, Lofberg R, Ekbom A. Risk of haematopoietic cancer in patients with inflammatory bowel disease. Gut 2005;54: 617–622
19. Bernstein CN, Blanchard JF, Kliewer E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer 2001;91: 854–862
20. Hemminki K, Li X, Sundquist J, Sundquist K. Cancer risks in ulcerative colitis patients. *Int J Cancer*. 2008;123: 1417–1421
21. Winther KV, Jess T, Langholz E, Munkholm P, Binder V. Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County. ClinGastroenterol Hepatol 2004;2: 1088–1095
22. Curtis JR, Lee EB, Kaplan IV, Kwok K, Geier J, Benda B, Soma K, Wang L, Riese R. Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancies across the rheumatoid arthritis clinical development programme. Ann Rheum Dis 2015;0:1–11