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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ABSTRACT

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 (b). 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 been 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
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.

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

**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 Tofacitinib 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

12. Troy Brown. EU Declines to Approve Tofacitinib (Xeljanz) for RA. Medscape Medical News. July 26, 2013