Original Study

Evidence for Clinical Differentiation and Differentiation Syndrome in Patients With Acute Myeloid Leukemia and IDH1 Mutations Treated With the Targeted Mutant IDH1 Inhibitor, AG-120

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Abstract

We describe 3 patients with relapsed/refractory acute myeloid leukemia who developed clinically-apparent differentiation concurrent with clinical response during monotherapy with AG-120, a novel oral inhibitor of mutant isocitrate dehydrogenase 1. Symptoms included marked leukocytosis and exuberant neutrophil recovery among other clinically apparent constitutional manifestations. Awareness of the potential for differentiation syndrome with such inhibitors, and prompt identification and intervention, are essential to facilitate clinical resolution.

Background: Cancer-associated isocitrate dehydrogenase (IDH) mutations block normal cellular differentiation via production of the oncometabolite, R-2-hydroxyglutarate. In patients with acute myeloid leukemia (AML) receiving targeted mutant IDH inhibitor therapy, neutrophil recovery within the setting of clinical differentiation syndrome (DS) has been anecdotally described. **Patients and Methods:** We describe 3 patients who developed clinically apparent DS during monotherapy with the mutant IDH1 inhibitor, AG-120, for relapsed/refractory AML. **Results:** AG−120-induced differentiation commenced within the first 60 days of treatment, notably in the same time frame as clinical response, strengthening the purported mechanism of targeted mutant IDH inhibitor therapy via successful myeloid maturation. Symptoms of DS were nonspecific and included culture-negative fever, edema, hypotension, malaise, and pleural and/or pericardial effusions, in addition to marked neutrophil-predominant leukocytosis. **Conclusion:** DS can occur during treatment with targeted mutant IDH1 inhibitor therapy. Patients might present with nonspecific clinical manifestations often in the setting of leukocytosis related to exuberant neutrophil recovery. Prompt identification and initiation of treatment interventions, including hydroxyurea, corticosteroids, and/or consideration of temporary treatment discontinuation, are important to facilitate prompt resolution.

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Introduction

Differentiation syndrome (DS) is a potentially fatal complication of effective leukemia treatment first described in patients with acute promyelocytic leukemia (APL) treated with all-*trans*-retinoic acid (ATRA).[1] The reported incidence in APL ranges from 2% to 27%,[2] likely because of the heterogeneity and range of clinical symptoms, as well as imprecise diagnostic criteria. In APL, signs and symptoms of DS have been described 2 to 47 days after treatment initiation, and include increasing white blood cell count (WBC) and absolute neutrophil count (ANC), culture-negative fever, weight gain, edema, dyspnea, interstitial infiltrates, pleural effusion, pericardial effusion, hypotension, and renal failure.[1,3,4] The underlying pathophysiology remains poorly understood, but is thought to be related to release of inflammatory vasoactive cytokines and tissue infiltration by briskly maturing cells.[2,5] Myeloid differentiation and clinical DS have also been described in patients with acute myeloid leukemia (AML) receiving therapy with fms-related tyrosine kinase 3 inhibitors and hypomethylating agents, including neutrophilic skin infiltrates retaining the aberrant *FLT3*-internal tandem duplication mutation in some instances.[6,7]

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Isocitrate dehydrogenase 1 and 2 (*IDH1* and *IDH2*) mutations are noted in approximately 20% of patients with AML.[8] Cancer-associated *IDH1/2* mutations block normal cellular differentiation and drive tumorigenesis by promoting abnormal reduction of α-ketoglutarate (α-KG) to the oncometabolite, R-2-hydroxyglutarate (2-HG).[9,10] 2-HG accumulation inhibits multiple α-KG-dependent dioxygenases, including histone and DNA demethylases, which regulate the cellular epigenetic state.[11] The first-in-human phase I clinical study of the novel, oral mutant IDH1 inhibitor, AG-120, is ongoing (ClinicalTrials.gov NCT02074839), and early results in 66 patients indicate that monotherapy is well tolerated, with an overall response rate of 36% according to International Working Group (IWG) criteria in a primarily relapsed/refractory AML population.[12] Responses occur without a period of bone marrow aplasia, unlike standard cytoreductive therapy.

Patients and Methods

Neutrophil recovery in the setting of a clinical DS in patients receiving mutant IDH inhibitor therapy has been anecdotally described, but the clinical patterns of differentiation have not been previously reported. Herein, we describe 3 patients treated at our institution who developed clinically apparent differentiation and DS during AG-120 monotherapy for relapsed/refractory AML.

Results

Case 1

A 53-year-old man was found to have incidental anemia during a routine physical examination. Results of complete blood count (CBC), bone marrow aspirate and biopsy, and cytogenetic and molecular studies at presentation are shown in Table 1. He received intensive cytarabine-based induction AML chemotherapy, which was associated with complications (Table 1) and end of cycle 1 staging bone marrow showed primary refractory disease with 77% myeloblasts.

Because of the presence of an IDH1-R132C mutation, the patient was transitioned to AG-120 500 mg/d orally on 28-day continuous cycles. His CBC on day 1 of therapy showed a WBC of 21.7 × 10^9/L, with 1% neutrophils and 95% circulating blasts (Table 1; Figure 1A). A day 14 bone marrow aspiration showed persistent AML, with 37% myeloblasts and at completion of cycle 1, blasts had reduced to 18% and he started cycle 2 without dose adjustments or treatment interruption (Table 1). On cycle 2, day 1, his WBC was 29 × 10^9/L with 24% neutrophils and 13% circulating blasts. On cycle 2, day 5, he reported a mild backache, and denied having fever, chills, cough, shortness of breath, nausea, vomiting, diarrhea, or urinary symptoms. His physical examination was normal except for mild 1+ nontender bilateral pedal edema. The CBC showed an increase in WBC to 42.5 × 10^9/L, with 64% neutrophils and 6% circulating blasts (Table 1; Figure 1A). There were no signs or symptoms of infection and he was maintained with empiric antimicrobial prophylaxis and hydroxyurea at 2 g/d was started. On cycle 2, day 8, he described symptoms of mild vertigo, poor appetite, and anorexia, and was found to be tachycardic and mildly hypotensive (100/59 mm Hg) with an otherwise unremarkable physical examination. An electrocardiogram (EKG) confirmed sinus tachycardia with no ST/T wave changes. An infectious evaluation including urine, sputum, and blood cultures was negative at 7 days. Hydroxyurea was reduced to 1 g/d. On cycle 2, day 12, the WBC was 12.4 × 10^9/L (76% neutrophils and 0% circulating blasts; Table 1). Hydroxyurea was discontinued 8 days after initiation. In the absence of any infectious etiology, the rise in leukocyte count with a predominance of mature neutrophils, concomitant reduction in circulating myeloblasts, platelet recovery, and mild clinical symptoms of hypotension, tachycardia, malaise, vertigo, and lower back pain that spontaneously resolved, were suggestive of DS.

The patient achieved a complete response after 3 cycles of AG-120 and transitioned to a matched related donor allogeneic stem cell transplant, and remains in an ongoing complete remission 2 months after transplantation with successful engraftment.

Case 2

Laboratory parameters for a 45-year-old man who presented with fatigue are shown in Table 1. He was treated with front-line AML induction therapy (Table 1). Because of primary refractory disease after cycle 1, he was treated with AG-221 (mutant IDH2 inhibitor) 100 mg daily for 4 cycles without evidence of response. He then received azacitidine (75 mg/m^2 intravenously on days 2-8) and nivolumab (3 mg/kg on days 1 and 14) as part of a clinical trial for 4 cycles without response.

Because of the persistence of his IDH1-R132C mutation, he started AG-120, 500 mg daily in the phase I trial. Laboratory parameters on cycle 1, day 1 are shown in Table 1 and included a WBC of 3.1 × 10^9/L with 6% neutrophils and 65% circulating blasts. Over the first 2 weeks of AG-120 treatment, peripheral myeloblasts steadily declined from 65% to 23% (Figure 1B). On cycle 1, day 19, he was hospitalized for acute onset chest pain and shortness of breath with exertion, without cough or upper respiratory complaints (vital signs and CBC are shown in Table 1, and included a WBC of 25.4 × 10^9/L with 39% neutrophils and 6% circulating blasts). An EKG showed sinus tachycardia and diffuse ST segment elevation concerning for pericarditis. A 2-view chest x-ray identified left lower lung opacities representing possible atelectasis or early pneumonia, with a small left pleural effusion and enlarged cardiac silhouette suggestive of pericardial effusion. The patient was admitted to the intensive care unit and empiric broad-spectrum antibiotics were started for possible pneumonia, prednisone 1 mg/kg for 3 days for pericarditis, and furosemide diuresis. An EKG on day 2 showed a sustained left ventricular ejection fraction of 59%, with a moderate to large pericardial effusion with no right ventricular chamber collapse. A repeat EKG 2 days later showed significant improvement in pericardial effusion with medical management. His clinical status improved and he was discharged after 5 days (cycle 1, day 23) with a further 1-week tapering course of steroids. AG-120 was continued during hospitalization and upon hospital discharge. All cultures during hospitalization were negative.

By cycle 2, day 1 of AG-120, the WBC had increased to 87.2 × 10^9/L with 40% neutrophils and 6% circulating blasts (Table 1, Figure 1B) and bone marrow blast count was stable (18%). Review of systems and physical examination were unremarkable. He received a 5-day course of hydroxyurea (2 g twice daily) to control leukocytosis. His WBC decreased over the next 2 weeks, normalizing by cycle 3, day 1 (Table 1). At that time, repeat assessment identified a complete remission with incomplete platelet recovery, with 3% myeloblasts in a