Case report

The use of low-dose protracted oral clofarabine in a patient with myelodysplastic syndrome after failing 5-azacitidine

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A B S T R A C T

Patients with myelodysplastic syndrome who fail hypomethylating agents have a very short median survival and about 25% risk of disease transformation to acute myeloid leukemia. We report our experience with low-dose protracted oral clofarabine in one patient who achieved stable disease for more than two years after failing 5-azacitidine.

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Myelodysplastic syndrome (MDS) is a group of clonal bone marrow disorders with increased risk for leukemic transformation. Aside from allogeneic stem cell transplantation, the currently approved treatments for MDS, including growth factors, lenalidomide and hypomethylating agents, are not curative and have short response duration. Further, after failure of hypomethylating agents, the median survival is very short-lived, only 4.3 months with similar 25% risk of progression to acute myeloid leukemia by one report. Another large study including 435 patients with high risk MDS that failed hypomethylating therapy demonstrated a median overall survival of 5.6 months and a two-year survival probability of only 15%. Of note, lack of hematologic response to previous hypomethylating therapy was one of the factors associated with poor outcome. Clofarabine is a second generation purine nucleoside analog that was tested in MDS both intravenously (IV) and orally. The IV route (15 mg/m2 daily for five days every 4 weeks) was administered in-house and was significantly myelotoxic. Only a median of two consolidation cycles were administered resulting in a median survival of 7.4 months. Since oral clofarabine has a bioavailability of 50% and could be administered in the ambulatory setting, it was tested in three different doses (20, 30 and 40 mg/m2 daily for five days every 4–8 weeks). A median of one consolidation cycle was administered to 31% of the patients with dose reduction in 74% of them due to infectious complications and prolonged myelosuppression. The median survival was 9.2 months. Most patients received the treatment in the ambulatory setting but 53% received growth factor support at some point and 50% developed infectious complications requiring hospitalization.

We hypothesized that protracted low-dose oral clofarabine will be more efficacious and less toxic and designed a phase I (I–144208, NCT01003678) trial to determine the safety and maximum tolerated dose of low-dose oral clofarabine daily for five days in a 28-day cycle. The initial dose was 1 mg as a fixed dose. Eligibility criteria included adult patients with intermediate- or high-risk MDS per the International Prognostic Scoring System Score (IPSS) who may have received up to two prior therapies and had adequate hepatic and renal function. The study was prematurely terminated by the company and we report here our experience with one patient on trial.

Case report

A 76 year-old Caucasian male who was evaluated in an emergency department due to headache in May 2001 and was found to have a right parietal subdural hematoma (SDH). Baseline blood work revealed thrombocytopeinia of 50 × 109/L. His SDH was managed with surgical evacuation with full recovery. He was then referred to our institute for evaluation of persistent thrombocytopeinia in August 2001 after recovering from a second SDH that was managed expectantly. His past medical history was limited to hypertension; he was a former smoker and he denied any chemical exposures, allergies or relevant family history. His initial white blood cell (WBC)
Romiplostim.6 These blasts did not correlate with the study drugs were continued. In spite of intermittently noticing cell transplant. As he was deemed ineligible to transplant, the peripheral blood for which he was evaluated for allogeneic stem into the study, he was noted to have circulating blasts in the marrow biopsy and aspirate on 03/08/2003 showed refractory anemia with an excess of blasts -1 with trilineage dysplasia, cellularity 65%, blasts 6.5% and normal male karyotype. It was mutually decided to continue observing until he was placed on erythropoietin 40,000 units subcutaneously weekly on 04/15/2005 for his anemia in addition to intermittent platelets transfusion averaging once a month for his thrombocytopenia.

He continued erythropoietin treatment until developing neutropenia with ANC of 0.7 × 10^9/L in August 2007; a repeated bone marrow biopsy and aspirate showed refractory anemia with excess of blasts-2 with 60% cellularity and 11% blasts. He was enrolled on protocol PH-93406 consisting of 5-azacitidine 75 mg/m² for seven days with or without AMG 531 (Romiplostim) on 28-day cycle starting his first on 09/01/2007 (he was randomized to both agents). He received a total of 15 courses of both 5-azacitidine and AMG 531 until the study closed in 12/09/2008. Six months into the study, he was noted to have circulating blasts in the peripheral blood for which he was evaluated for allogeneic stem cell transplant. As he was deemed ineligible to transplant, the study drugs were continued. In spite of intermittently noticing circulating blasts ranging between 2 and 7%. The occasional peripheral blood blasts could be explained by the effect of Romiplostim.4 These blasts did not correlate with the findings on the repeated bone marrow biopsy and even at the end of study biopsy (12/19/2008) that showed persistent MDS with 40% cellularity and only 2% blasts. Due to closure of the study, his therapy was changed to 5-azacitidine 75 mg/m² for five days on 28-day cycle; first dose received on 01/02/2009. He finished 9 cycles by 10/17/2009 with worsening of transfusion requirement (up to twice a week, with Hgb ranges 7.0–8.5 g/dl and platelets count between 10 and 20 × 10^9/L) and worsening neutropenia (ANC 0.5–0.7 × 10^9/L).

The patient was enrolled on protocol I-144208 consisting of low dose clofarabine 1 mg (fixed dose) orally daily for five days on 28-day cycle. His baseline bone marrow aspirate and biopsy on 11/19/2009 was consistent with persistent MDS with 70% cellularity and 3% blasts. His first cycle was complicated by a one-week admission for neutropenic fever with negative bacterial cultures. After two more cycles (March 2010) he had an episode of Staphylococcus Epidermis and Serratia Liquefaciens bacteremia that was successfully treated with IV antibiotics. His treatment continued for a total of 32 cycles by the time of this report, complicated by grade 1 transaminitis and grade 1 rash on lower extremities. He continues to be transfusion-dependent, receiving platelets on average once a week and red blood cells once or twice a month. He has reasonable quality of life and functional capacity with estimated Karnofsky score of 70%.

To the best of our knowledge, only one other group7 studied low-dose protracted oral clofarabine in MDS patients who failed hypomethylating agents. They studied 5 mg (fixed dose) daily for 10 consecutive days of a 28-day cycle. All patients who were treated for 10 days had a greater than 25% drop in their baseline counts with cycle one and received only seven days of treatment in subsequent cycles. The protocol was then modified to administer clofarabine for seven days which did not result in any significant toxicity. That study was prematurely terminated by the company after 19 patients were enrolled.

This case demonstrates the potential of using protracted low-dose oral clofarabine in patients who failed hypomethylating agents, a group of patients with extremely poor outcome.2,3 We therefore propose that protracted low-dose oral clofarabine be studied in this patient population.

Contributions

Dr. Al Ustwani followed the case and wrote the manuscript, Ms. Greene was the research coordinator who collected the data and Dr. Wetzler was the Principal Investigator and supervised the conduct of the trial.

All authors read the final version of the manuscript and approved it.

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