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Short Communication

Long-term 5-azacitidine for post stem cell transplant relapse prevention and maintenance

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ABSTRACT

Chronic Myelomonocytic leukemia (CMML) is a rare disease that has an annual incidence rate of 0.83-1 case per 100,000 people and generally impacts the elderly population. Therapeutic options for patients with CMML especially after relapse are limited. We present a case of a 77-year old female who was diagnosed with CMML in June, 2003. Patient underwent induction chemotherapy with Topotecan and Fludarabine but failed to achieve complete remission (CR). In January, 2004 she underwent her first matched related donor hematopoietic bone marrow stem cell transplant (SCT) after conditioning with Fludarabine and Busulfan. Patient relapsed in May 2005 after which she received 5-azacitidine and Cytarabine; while she achieved hematological remission, her bone marrow showed persistent dysplasia. She received her second matched donor related SCT in September 2005 after conditioning with Melphalan and Fludarabine. The post-transplant course was uneventful and monthly 5-azacitidine maintenance therapy was initiated 2 months after transplant. Fourteen years later the patient remains on maintenance 5-azacitidine and continues to be in full remission. Due to the length of her treatment with 5-azacitidine herein we describe the long-term use of 5-azacitidine post-SCT and its impact on CMML patients.

KEYWORDS: Vidaza, stem cell transplantation, maintenance therapy.

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INTRODUCTION

Chemotherapy is increasingly administered following hematopoietic bone marrow stem cell transplant (SCT) for the purposes of relapse prophylaxis. Hypomethylating agents are typically utilized for this purpose and continue for one year's duration. The optimal duration for post SCT relapse prophylactic chemotherapy is unknown. Herein we describe a case of a patient who continues to receive post SCT relapse prophylaxis at fourteen years following SCT.

CASE REPORT

A 77-year old female with the initial diagnosis of myelodysplastic syndrome was admitted to the hospital in June 2003. She presented with mild anemia with hemoglobin of 10.6 g/dL. She subsequently had a bone marrow biopsy that revealed myelodysplastic syndrome/CMML with poor prognostic factor of cytogenetics showing a t(X;11). She was treated with Topotecan and Fludarabine induction but failed to reach complete remission. Therefore, she agreed to proceed with protocol DM99-251 with a matched related stem cell transplant. Furthermore, she agreed to be enrolled in a high dose versus low dose tacrolimus randomized study DM03-0210. She was admitted into the hospital in January, 2004 for high dose chemotherapy which included 5-Flurouracil, Doxorubicin, Mitomycin-C, and Cisplatin (FAMP) 30 mg/meters^2 for three days, 3.2 mg/kg of Busulfan for three days and 1 day of 1.6 mg/kg of Busulfan. She then received an allogeneic peripheral blood stem on January 28, 2004.

She tolerated this treatment well with no difficulty. Patient was discharged in February of 2004. However, the post-transplant course was complicated by graft versus host disease (GVHD) of the skin and eyes, which responded to steroid therapy. The patient relapsed in May of 2005 and she began treatment with 5-azacitidine and Cytarabine in July of 2005. She tolerated this treatment well achieving complete hematologic remission; however, there was persistent dysplasia in the bone marrow. She then received her second matched related donor hematopoietic stem cell transplant after conditioning with melphalan and Fludarabine. The post-transplant course was uneventful and she was maintained on 5-azacitidine dosed monthly at 32 mg/m^2, less than half of the normal dosage of 75 mg/m^2 of 5-azacitidine (wells). The patient continues to follow monthly in clinic and remains on maintenance 5-azacitidine. The patient is in complete remission.

DISCUSSION

CMML is a myeloid disorder that exhibits both myeloproliferative and myelodysplastic features with associated chronic monocytosis [1]. It usually occurs in the elderly over the age of 70 with overall poor prognosis [1]. The World Health organization (WHO) uses 2 prognostic factors to risk stratify patients namely WBC counts and blast cell percentage [2]. Depending on blast percentage CMML is further classified to CMML-0, CMML-1 CMML-2. Allogeneic stem cell transplants are the only known curative form of treatment for CMML; however, relapse rates are about 20% for standard risk patients and 40-80% for high risk patients [3]. Other existing treatments, depending on the blood cell counts, are cytoreductive treatment with hydroxyurea for proliferative features, or the use of erythropoiesis stimulating treatment for anemia and dysplastic features. Hypomethylating agents have also been used for treatment of CMML. Azacitidine and Decitabine are two such hypomethylating agents. Azacitidine is administered to patients with high risk myelodysplastic syndrome. These types of patients receive a median of 3 cycles of azacitidine to achieve first response; however partial or complete remission may require more than 3 cycles [4]. Furthermore, azacitidine can be continued as long as the patient receives continued benefits as there is a lack of alternative treatment options. Azacitidine is usually well tolerated. The usual adverse effects include myelosuppression, nausea, diarrhea, constipation, and local site reactions [5]. Renal and liver toxicity are also known side effects [5]. Overall response rates of 40-60% have been reported with azacitidine use [6]. Complete response however is about 15% with an overall median survival of 12-37 months after the commencement of the treatment [6]. Azacitidine treatment is FDA approved specifically for CMML nonproliferative type. Treatment with azacitidine is continued if there is response due to lack of other alternatives.

CONCLUSION

Our patient received azacitidine for about 14 years, which is the longest known use for maintenance post SCT therapy and she continues to be in complete remission. Her continuation of 5-azacitidine was a viable treatment option because she relapsed twice post-transplant and her counts have remained stable while she has been on maintenance 5-azacitidine. This evidence warrants further studies into the long-term use of 5-azacitidine as a chemotherapy agent in other myelosuppressive conditions.

STATEMENT OF ETHICS

Not applicable as this is a case review manuscript.

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AUTHOR CONTRIBUTIONS

Tanmay Srinivasan and Amanda Olson contributed equally to the writing of this manuscript. Melissa Barnett edited the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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