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Indefinite Azacitidine Treatment Until Progression May Provide Long-Term Disease Control in Elderly Patients with Acute Myelogenous Leukemia

Progresyona Kadar Devamlı Azasitidin Tedavisi, Yaşlı Akut Miyeloid Lösemililerde Uzun Süreli Hastalık Kontrolü Sağlayabilir

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ABSTRACT

The prognosis of acute myelogenous leukemia (AML) is poor in elderly patients. The mean survival rates at second and fifth years for AML were 10% and 2%, respectively. Here our aim was to demonstrate that the survival rate can be prolonged by long-term azacitidine (AZA) treatment. Complete remission was achieved at the end of the fourth and sixth courses of AZA treatment in three elderly patients with AML with a high blast count. The first patient was followed without any treatment after getting complete remission with four courses of AZA, and at the end of 1 year follow-up, the patient died due to pneumonia. Complete remission was obtained in the second and third patients after four and six courses of AZA, respectively. Second patient is still being followed up in complete remission at the end of the 20th course of AZA. Recurrence occurred at the end of the 16th AZA course in the third patient and he died after 20 months of the treatment. In elderly patients with AML with a high blast count, the continuation of AZA treatment improves the overall survival rates.

Keywords: Elderly, acute myelogenous leukemia, azacitidine

ÖZ

Yaşlı hastalarda akut myeloid löseminin (AML) prognozu kötüdür. İki ve 5 yıllık ortalama sağ kalım oranları sırasıyla %10 ve %2'dir. Burada amacımız uzun süreli azasitidin tedavisi ile sağ kalımın uzadığının gösterilmesidir. Yüksek blast sayılı 3 yaşlı AML hastasında 4. Ve 6. Kürler sonunda tam remisyon elde edildi. Birinci olguda 4 kür tedavi ile remisyon elde edildikten sonra tedavisiz izlendi. Bir yıl sonunda nüks gelişen hasta pnömoni nedeniyle öldü. İkinci ve 3. olguda sırasıyla 4 ve 6 kür sonunda tam remisyon elde edildi. İkinci olguda 16. Kür sonunda nüks gelişti. Üçüncü olgu ise tedavisinin 16. Ayında halen remisyonda izlenmektedir. Yüksek blast sayılı yaşlı AML hastalarında azasitidin tedavisine devam edilmesi sağ kalım süresini artırmaktadır.

Anahtar Kelimeler: Yaşlı, akut myeloid lösemi, azasitidin

Introduction

Acute myelogenous leukemia is an aggressive disease with a poor prognosis (1). The expected overall survival (OS) rates at 2 and 5 years are 10% and 2% in elderly patients, respectively (2). Therapeutic options are limited in this population (3). Therapy related mortality rates increase up to 10%-25% due to poor performance status, comorbidities, adverse cytogenetics, and frailty (4). Low dose cytarabine, tipifarnib-a farnesyl transferase inhibitor, and gemtuzumab ozogamycine have limited impact on OS. The survival advantage of clofarabine is yet to be proven (5-7). The median survival with intensive chemotherapy is 5-13 months (4, 7). Azacitidine (AZA) has been shown to significantly increase OS in a recent phase III study compared with conventional regimens in the treatment of intermediate-2 and high-risk MDS patients with a blast count of 20%-30% (7). Here we present three elderly patients with AML who presented with a high (>30%) blast count and had complete response with initial AZA treatment. Two of them achieved longer disease-free survival with azacitidine maintenance.

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Case Reports

Case 1

A 71-year-old male patient was admitted to our clinic with complaints of malaise, fever, and cough. Bone marrow aspiration showed 61% of blasts with folded large nuclei, basophilic cytoplasm, and no granules. Bone marrow biopsy revealed diffuse infiltration of blasts. CD33, CD14, CD11b, HLA DR, and myeloperoxidase were positive and CD34 was negative in flow cytometric analysis. He had normal karyotype. No genetic abnormality was reported in fluorescence in situ hybridization (FISH) and mutational analyses. He was diagnosed with standard risk AML. Because of his advanced age and frailty, which was assessed using the G8 frailty score, he was not considered for an intensive therapy, and AZA therapy was initiated. At the end of four cycles, the bone marrow blast percentage was 3%. Peripheral blood counts were normalized as follows: leukocytes, 8,200/μL; hemoglobin, 14.4 g/dL; and platelets, 240,000/μL. The patient had complete remission during the next 12 months with no further treatment. After a year of follow-up, the disease relapsed and the patient died of pneumonia (Figure 1). The patient's consent could not be obtained because of death.

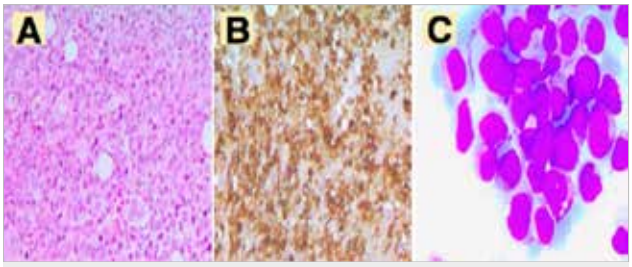

Figure 1. a-c. Bone marrow biopsy and aspiration at the time of diagnosis. (a) Bone marrow biopsy showing blastic cell infiltration (×400, H&E stain). (b) Immunohistochemistry showing lysosyme immunoreactivity in most blastic cells (×400, Lysosyme stain). (c) View of myeloblasts on the bone marrow aspiration smear (×1000, Giemsa stain)

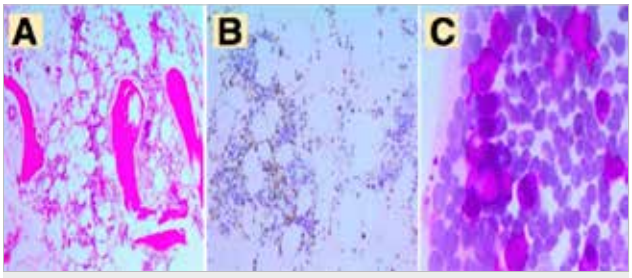

Figure 2. Bone marrow biopsy and aspiration after six cycles of azacitidine treatment. (a) Bone marrow biopsy showing granulocytic and erythroid cell precursors (×100, H&E stain). (b) Immunohistochemistry showing myeloperoxidase immunoreactivity in granulocytic cells (×200, Myeloperoxidase stain). (c) View of normal granulocytic and erythroid cell precursors on the bone marrow aspiration smear (×1000, Giemsa stain)

Case 2

A 74-year-old female with a history of rheumatoid arthritis and hypertension presented with malaise. She was taking nonsteroid anti-inflammatory drug and methotrexate for her comorbid conditions. At presentation, her complete blood counts were leukocytes, 25,000/μL; hemoglobin, 7.2 g/dL; and platelets, 19,000/μL. Bone marrow biopsy and aspiration revealed that 65% of the bone marrow cells were monoblasts with fine chromatin, granular cytoplasm, and no Auer rods (Figure 2). Flow cytometry showed that 72% of the cells in blast gate expressed CD13, CD33, CD14, HLADR, CD117, and myeloperoxidase positive monoblasts (Figure 1). Conventional cytogenetics, FISH, and mutational analysis showed normal karyotype. She was diagnosed with standard risk AML. The Charlson comorbidity index score was 2. She was not considered eligible for intensive chemotherapy and received AZA, and at the end of four cycles, complete response was achieved. The blast count in the bone marrow was 1% (Figure 2). The peripheral blood count was normalized with a leukocyte count, 6,700/μL; hemoglobin, 12.5 g/dL; and platelets, 242,000/μL. AZA maintenance was commenced upon the off-label approval of the government health authority. Her treatment is ongoing, and she is in complete remission after 20 cycles of AZA. The patient's consent was taken by her daughter.

Case 3

A 67-year-old male was referred to our clinic for his complaints of weight loss and accompanying pancytopenia (leukocytes, 1900/μL; hemoglobin, 8.2 g/dL; and platelets, 65,000/μL). Bone marrow biopsy showed significant dysplasia in all cell lines and erythroid hyperplasia. Further, 42% of his bone marrow cells were myeloblasts with folded nuclei, prominent nucleoli, narrow cytoplasm, no granules, and no Auer rods. In flow cytometric analysis, myeloblasts expressed CD34, HLADR, CD117, CD13, and myeloperoxidase. Although a cytogenetic abnormality due to significant dysplastic morphology was expected in his bone marrow, conventional cytogenetics, FISH, and mutational analyses reported normal karyotype. The patient was diagnosed with standard risk AML, possibly transformed from myelodysplastic syndrome. Because he was frail, he was commenced on AZA treatment. The bone marrow blast count was 1.5% after six cycles of treatment. Complete blood count revealed leukocytes, 9,500/μL; hemoglobin, 13.4 g/dL; and platelets, 191,000/μL. Off-label approval was obtained for AZA maintenance. Recurrence occurred at the end of the 16th AZA course and he died after 20 months of treatment. The patient's consent could not be obtained because of death.

Discussion

The only curative treatment options in AML are conventional intensive and high dose chemotherapy followed by stem cell transplantation. These are rarely performed in elderly patients

because of their poor performance status, frailty, and comorbidities. AZA was approved for the treatment of AML with 20%-30% bone marrow blast counts (7). The ongoing AZA-001 study will provide more information on the activity of AZA in this population.

Fenaux et al. have reported that AZA treatment is more superior to conventional chemotherapy in patients with low-blast-count AML according to the WHO classification (7). In contrast, although AZA treatment in elderly patients with AML has been shown to be safe and effective, OS was not significantly different in patients with a high percentage of bone marrow blasts exceeding 30% (8). The first response to AZA is achieved following at least median three cycles of treatment (7). However, most responses are achieved after six cycles, and 92% of the patients have best responses after 12 cycles of treatment (9).

Considering published data, although the beneficial effects of AZA shortly occur, additional cycles are usually necessary. The discontinuation of treatment after the best response is followed by the reemergence of aberrant promoter methylation and gene silencing. Therefore, treatment continuation offers the best chance to improve response as long as the treatment is well tolerated and the disease is under control (7, 10).

Conclusion

Here we presented three elderly patients with AML who had high marrow blast counts. These patients were not eligible for intensive treatment options. While the best responses were observed in all with only four to six cycles of therapy, long-term disease-free survival was provided by the indefinite use of AZA. Considering the dismal prognosis of AML in elderly patients, increased treatment-related mortality associated with intensive chemotherapy in this population, and poor survival after the relapse, which is an inevitable consequence of AZA discontinuation in responding patients, it is reasonable to continue AZA until progression in responders.

Informed Consent: The patient's consent could not be obtained because of death.

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