***Case Report* / Olgu Sunumu**

Amifostine Treatment of a Patient with Refractory Acute Myeloid Leukemia

Dirençli Akut Myeloid Lösemi Hastasının Amifostin ile Tedavisi

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The prognosis for the majority of acute myeloid leukemia (AML) patients without a donor is dismal whether conventional salvage chemotherapy regimens or investigational strategies are used, and most of these patients will eventually die of their disease. There is no standard chemotherapy regimen that provides durable complete remission in patients with refractory AML. Beneficial effects of amifostine, either alone or in combination with conventional chemotherapy, was demonstrated in patients with myelodysplastic syndrome and poor prognosis AML. Here we report our second experience with AML patients who were successfully treated with an amifostine containing noncytotoxic drug combination. The beneficial effects of amifostine are not limited to cytoprotectivity which enables dose-escalation for many chemotherapeutic agents, at least in some refractory AML it can also be used as a bridge to hematopoietic stem cell transplantation.

Key words: Acute myeloid leukemia; amifostine.

İster konvansiyonel kurtarma kemoterapileri istersе araştırma temelli stratejiler kullanılsın, vericisi olmayan çoğu akut myeloid lösemi (AML) hastasının prognozu kötüdür ve bu hastaların çoğu hastalıkları nedeniyle kaybedilir. Dirençli AML hastalarında kalıcı tam yanıt sağlayan standart bir kemoterapi rejimi yoktur. Amifostinin tek başına ve konvansiyonel kemoterapiler ile birlikte kullanımının myelodisplastik sendrom ve kötü prognozlu AML hastalarında yararlı etkileri gösterilmiştir. Burada amifostin içeren sitotoksik olmayan ilaç kombinasyonu ile başarıyla tedavi edilen AML hastalarındaki ikinci deneyimimizi bildiriyoruz. Amifostinin yararlı etkileri birçok kemoterapi ilacının doz artımına olanak sağlayan hücre koruyuculuğu ile sınırlı değildir ve en azından bazı dirençli AML hastalarında kök hücre nakli için bir köprü olarak kullanılabilir.

Anahtar sözcükler: Akut myeloid lösemi; amifostin.

The definition of refractory acute myeloid leukemia (AML) includes patients who fail standard induction chemotherapy, those with a short (less than 6-12 months) first complete remission (CR1), and patients who have relapsed twice or more.[1] Allogeneic hematopoietic stem cell transplantation (HSCT) is the only known curative treatment option for patients with AML. The prognosis for the majority of AML patients without a donor is dismal whether conventional salvage chemotherapy regimens or investigational strategies are used, and most of these patients will eventually die of their disease. There is no standard chemotherapy regi-

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men that provides durable CR in patients with refractory AML.

Amifostine, a phosphorylated sulphydryl compound, was developed to protect tissues from toxic side effects of ionizing radiation and of a variety of cytotoxic drugs, including cisplatin, carboplatin, nitrogen mustard and cyclophosphamide.[2] Amifostine is a prodrug, which is converted to its active metabolite (WR-1065) by tissue bound alkaline phosphatase. In the presence of chemotherapy free thiol in amifostine behaves as a scavenger of oxygen-free radicals. Because normal cells rather than tumor cells have higher alkaline phosphatase activity and WR-1065 diffuses easier to the cell with normal pH, there is no decrease in the antitumoral effect of cytotoxic drugs while cytoprotectivity is observed in normal tissues.[3]

Besides protective effects mentioned before, amifostine has some important features which make it useful in the treatment of patients with hematologic malignancies. Amifostine stimulates in vitro proliferation of hematopoietic progenitors and improves hematopoiesis in myelodisplastic syndromes (MDS).[4,5] It was also found to suppress apoptosis, TNF-α, IL-6 transcription and telomerase expression in AML patients.[6,7] Beneficial effects of amifostine, either alone or in combination with conventional chemotherapy, was demonstrated in patients with MDS and poor prognosis AML.[3,7-10]

Here we report our second experience with AML patients who were successfully treated with an amifostine containing noncytotoxic drug combination.

CASE REPORT

A 43-year-old male patient was diagnosed as AML on January 2005. Morphologic, cytochemical and flow cytometric analysis of peripheral blood and bone marrow revealed AML-M1. Cytogenetic examination of bone marrow showed normal karyotype. HLA typing of his family members (4 brothers and 4 sisters) revealed any matched-related donor suitable for allogeneic HSCT. Following induction chemotherapy including mitoxantrone 12 mg/m^2 D1-3 and cytosine arabinoside 100 mg/m^2 D1-7 (3+7), first complete remission (CR1) was achieved. He received three courses of standard dose ARA-C (100 mg/m^2 D1-7) as consolidation treatment. Six months later after completion of his last consolidation course the patient relapsed. He was successfully treated with a fludarabin and high-dose ARA-C containing regimen (FLAG). Following second CR, he received four courses of consolidation chemotherapy consisting 6 g/m^2/d ARA-C for three days (HiDAC). During HiDAC cycles he had two life-threatening infections, one *E. coli* sepsis and one culture negative pneumonia, respectively. Nine months after his last chemotherapy the patient relapsed again. At this time the patient did not respond to 3+7 induction chemotherapy. During his last hospitalization he required treatment with broad spectrum antibiotics and antifungal agents for pneumonia and septic shock. As the patient refused further cytotoxic chemotherapy, we decided to go on with amifostine. Amifostine was administered intravenously 200 mg/m^2 three times a week, with ciprofloxacin 500 mg/d, pentoxifylline 1200 mg/d and dexamethasone 4 mg/d orally. After two weeks of treatment the patient achieved his third CR. He completed eight weeks of therapy without interruption. He didn't receive any form of consolidation chemotherapy thereafter. At the time of the preparation of this manuscript the patient was still in continuous CR with normal blood counts and this remission was maintained through 12 months.

DISCUSSION

This is our second experience with AML patients who were successfully treated with an amifostine containing noncytotoxic drug combination.[3] As the self-renewal capacity and immortalization of leukemia cells are highly dependent on the level of telomerase enzyme, the inhibitory effect of amifostine on telomerase activity seems to play an important role in reducing proliferative potential of malignant cells.[6] The beneficial effects of amifostine are not limited to cytoprotectivity, making dose-escalation possible for many chemotherapeutic agents. At least in some refractory AML it can be used as a bridge to HSCT.

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