Amifostine treatment in patients with myelodysplastic syndrome

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ABSTRACT

Myelodysplastic syndrome (MDS) is a clonal disorder that is characterized by peripheral cytopenia and the induction of apoptosis is thought to be partially responsible for pathological haematopoiesis in MDS. Amifostine is a cytoprotective and antioxidant agent, and it may prolong the survival of progenitor cells in MDS by delaying apoptosis. The study has been carried out with 9 MDS cases. Four of them were diagnosed as refractory anemia (MDS-RA), two as refractory anemia with ring sideroblasts (MDS-RARS) and the remaining three as refractory anemia with excess blasts (MDS-RAEB) according to the French-American-British (FAB) classification. Amifostine was given in a dose of 400 mg/m^2, as an IV infusion administered in 5-6 minutes, three times a week for 4 consecutive weeks. Three of the cases (33.3%), two with MDS RARS and one with MDS-RA, showed a significant improvement in the number of total leukocyte, neutrophil and reticulocyte counts and a decrease in the requirement of erithrocyte transfusions. In clinically responsive cases, all hematological parameters returned back to pre-treatment values two weeks after the cessation of therapy. We conclude that Amifostine can be used in a selected group of patients with MDS-RA and MDS-RARS.

Key Words: Myelodysplastic syndrome, Amifostine.

ÖZET

Miyelodisplastik sendromlu hastalarda amifostin tedavisi

Miyelodisplastik sendrom (MDS), klonal bir hastalık olup periferik sitopeni ve apopitozis indüksiyon artışının kısmen sorumlu olduğu patolojik hematopoiezis ile seyreder. Amifostin, sitoprotektif ve antioksidan bir ajan olup, MDS olgularında apopitozisi geciktirerek progenitör hücre yaşam süresini uzatabilmektedir. Bu çalışma, Fransız-Amerikan-İngiliz (FAB) sınıflandırmasına göre 4 MDS- refrakter anemi (MDS-RA), 2 MDS-ring sideroblast ile refrakter anemi (MDS-RARS) ve 3 MDS-artmış blast sayısı ile dirençli anemi (MDS-RAEB) olgusu olmak üzere toplam dokuz olgu ile gerçekleştirilmiştir. Amifostin olgulara 400 mg/m^2, beş-altı dakikada intravenöz yolla dört ardışık hafta boyunca ve haftada üç kez uygulanmıştır. Üç (%33.3) olgunun biri MDS-RA ve ikisi MDS-RARS-tedavi son-

rası lökosit, nötrofil ve retikülosit sayılarında belirgin bir artış izlenmiş ve eritrosit transfüzyon gereksinimleri azalmıştır. Klinik yanıt alınan bu olgularda ilacın kesilmesi ile tüm parametreler tedavi öncesi değerlere geri dönmüştür. Amifostin kullanımının MDS-RA ve RARS olgularında sınırlı bir etkinliği olabileceği sonucuna varılmıştır.

Anahtar Kelimeler: Miyelodisplastik sendrom, Amifostin.

INTRODUCTION

Myelodysplastic syndrome (MDS) is a clonal disorder that is characterized by peripheral cytopenia due to ineffective hematopoiesis, despite increased bone marrow cellularity. It is proposed that induction of apoptosis is partially responsible for the pathological haematopoiesis in MDS patients[1-3]. Increase of apoptosis in MDS patients is thought to be brought about by some extracellular hematopoietic inhibitor cytokines such as tumor necrotizing factor-alpha (TNF-α)[4]. In fact, it has been demonstrated that the intracellular oxygen free radical production was increased in CD34+ stem cells and that was attributed to the increase in TNF-α concentration in MDS[5].

Amifostine protects the bone marrow progenitor cells from the adverse effects of ionizing radiation and cytotoxic treatment, and thus is used as a cytoprotective agent in patients undergoing chemotherapy and/or radiotherapy[6,7]. In canine models, amifostine stimulates hematopoiesis and causes an increase in the leukocyte, thrombocyte and reticulocyte counts and hematocrite values[8]. Due to the thiol group in its chemical structure, amifostine can act as an antioxidant[6,7]. Because of this effect, the survival of progenitor cells may increase, and this in turn is related to the delay of apoptosis in MDS patients[3,5]. Although there are contradictory reports in the literature, in a small number of cases it has been demonstrated that amifostine administration improved the cytopenias of MDS patients[9-11].

In this study, the effect of amifostine in cytopenic MDS patients was evaluated.

MATERIALS and METHODS

This retrospective study was performed in Marmara University and Karadeniz Technical University, Schools of Medicine, Departments of Hematology. A total number of 9 patients were included in the study. Four of these patients had refractory anemia (MDS-RA), 2 had refractory anemia with ring sideroblast (MDS-RARS) and the remaining 3 had refractory anemia with excess blast (MDS-RAEB), all of whom fulfilled the inclusion criteria shown in Table 1. Five of the patients were male and 4 were female. The median age of the patients was 67.6 ± 15.8 (38-84). Complete blood and reticulocyte counts and "absolute" neutrophil counts were performed before and during the amifostine therapy weekly in all cases. The threshold values for transfusion requirements were determined to be 8 g/dL for haemoglobin and 10 x 10^9/L for platelet levels.

Amifostine (Ethyol®, 500 mg) was administered in a dose of 400 mg/m^2 by IV infusion within 5-6 minutes, 3 doses per week, for a total of 4 consecutive weeks. Criteria for the treatment response are shown in Table 2.

Table 1. Inclusion criteria

1. Blast in bone marrow < 10%
2. Karnofsky score ≥ 50%
3. Haemoglobin level ≤ 10 g/dL (for the patients who had no previous erythrocyte transfusions)
4. Two or more units of erythrocyte or thrombocyte transfusion requirements per month
5. Platelet counts ≤ 100 x 10^9/L
6. Neutrophil counts ≤ 0.5 x 10 x 10^9/L

Table 2. Criteria for the response of the treatment

1. Increase in haemoglobin ≥ 1.5 g/dL (without transfusion).
2. ≥ 50% reduction in erythrocyte transfusion requirements as compared with pre-treatment requirements.
3. ≥ 50% reduction in platelet transfusion requirements as compared with pre-treatment requirements in transfusion dependent patients (platelet count ≤ 10 x 10^9/L).
4. 50% increase in baseline platelet counts of the transfusion independent patients (platelet counts ≥ 10 x 10^9/L). In this group, increase in platelet counts must exceed the 15 x 10^9/L level after treatment.
5. ≥ 50% increase in baseline "absolute" neutrophil counts.

All patients were transfusion-dependent and did not receive any treatment during the amifostine therapy.

Parameters during and after amifostine treatment were compared statistically using Mann Whitney U test, and $p< 0.05$ was accepted as significant.

RESULTS

All patients were available for the evaluation of the therapeutic response and toxicity during the treatment and two weeks after discontinuation of amifostine. The pre- and post-treatment hematological parameters of the patients are shown in Table 3.

Three of the cases (33.3%) showed significant responses according to the treatment response criteria. Responding patients sho-

Table 3. Pre- and post-treatment values of the hematologic parameters of all patients

Number of the patients	**1***	**2***	3	4	5	**6***	7	8	9
Age and gender	**52, M**	**84, F**	**80, F**	**70, F**	**75, M**	**77, F**	**60, M**	**35, M**	**76, M**
FAB types of MDS	RA	RARS	RA	RAEB	RAEB	RARS	RA	RA	RAEB
Total leukocyte counts									
Pre-treatment (10^9/L)	4.5	5.3	1.4	1.2	4.8	3.8	11.7	17.1	4.0
Post-treatment (10^9/L)	8.0	9.3	2.0	1.2	5.0	5.3	18.6	16.0	5.1
Neutrophil counts									
Pre-treatment (10^9/L)	2.2	2.5	0.7	0.6	2.5	1.2	5.2	6.5	1.8
Post-treatment (10^9/L)	4.4	6.4	1.3	0.5	2.1	4.5	6.1	8.5	2.3
Hemoglobin concentration									
Pre-treatment (g/dL)	9.0	6.3	8.3	9.4	8.0	7.6	3.9	6.0	5.6
Post-treatment (g/dL)	12.5	8.5	6.7	7.3	7.8	9.3	4.0	6.0	6.7
Reticulocytes									
Pre-treatment (%)	-	0.7	0.7	-	-	0.5	0.4	0.2	2.0
Post-treatment (%)	8.9	2.3	0.9	-	-	2.5	0.2	0.4	2.0
Platelet counts									
Pre-treatment (10^9/L)	38	346	5	13	35	245	32	18	160
Post-treatment (10^9/L)	109	449	9	21	40	260	34	6	182
ES** requirement/month									
Pre-treatment	1	5	10	1	4	5	6	6	8
Post-treatment	0	2	8	1	3	0	8	8	2
TS*** requirement/month									
Pre-treatment	0	0	8	8	0	0	4	8	0
Post-treatment	0	0	8	12	0	0	4	12	0

* Patients 1, 2, and 6 are responders.
** ES: Erythrocyte suspension.
*** TS: Thrombocyte suspension.

wed a significant improvement in the number of total leukocyte, neutrophil and reticulocyte counts and there also was a decrease in the requirement of red blood cell transfusions (Table 4). Patients who had advanced stage MDS did not respond to amifostine treatment. When responders and non-responders were evaluated together, there were no statistically significant changes in the pre- and post-treatment values of the above parameters (Table 5).

The drug was well tolerated by all patients and no adverse effect was observed.

In clinically responsive cases, all hematologic parameters returned back to pre-treatment values two weeks after the cessation of therapy.

DISCUSSION

The use of recombinant hematopoietic cytokines, retinoids and vitamin D3 in supraphysiologic doses may stimulate normal hematopoiesis and enhance the "survival" and maturation of progenitor cells in MDS patients[12-20]. However, the response rates of cytokine treatments is not so good in MDS patients.

It has been reported that amifostine administration in MDS delays apoptosis in CD34+ cells which are sensitive to oxidant stress (anti-apoptotic effect), and increases the survival of progenitor cells[3,5]. These findings set the ground for the hypothesis that amifostine might be effective in the treatment of MDS cases. Our findings show that amifostine treatment induces hematopoiesis in a subgroup of MDS patients. Similar fin-

Table 4. Average hematologic parameters of the 3 responders

	Pre-treatment	Post-treatment
Total leukocyte counts (10^9/L)	4.5	7.5
Neutrophils (10^9/L)	1.9	5.1
Hemoglobin (g/dL)	7.6	10.1
Reticulocytes (%)	1.9	4.5
Platelets (10^9/L)	209	272
ES requirement/month	3.7	0.7
TS requirement/month	0	0

ES: Erythrocyte suspension, TS: Thrombocyte suspension.

Table 5. Average hematologic parameters of all 9 patients

	Pre-treatment	Post-treatment	p value
Total leukocyte counts (10^9/L)	5.9	7.8	NS
Neutrophils (10^9/L)	2.5	4.0	NS
Hemoglobin (g/dL)	7.1	7.6	NS
Reticulocytes (%)	1.2	1.9	NS
Platelets (10^9/L)	97.5	120.2	NS
ES requirement/month	4.4	3.5	NS
TS requirement/month	3.5	4.8	NS

ES: Erythrocyte suspension, TS: Thrombocyte suspension, NS: Non-significant.

dings were obtained for the first time by Listz et al who showed significant recovery in the hematologic parameters of single or multilineage hematopoietic series in 15 of 18 MDS patients (83%), with amifostine treatment[10]. Following this article, other studies have been published which claimed that amifostine could be effective especially in the low-risk MDS patients when given in doses of 200-400 mg/m^2 IV. Amifostine increased the hemoglobin concentration, reticulocyte and neutrophil counts[21-30]. In some of these studies, amifostine was used in combination with other hematopoietic growth factors and/or dexamethasone. Raza et al reported that cytopenias in 22 of 29 MDS patients recovered after using amifostine combined with other antioxidant agents, namely pentoxyphylline, ciprofloxacin and dexamethazone[22]. Yet, the results of these studies are not convincing that combination therapies enhance the effectiveness of amifostine[22,26,28].

When our study is assessed together with the above literature, it can be claimed that amifostine primarily effects the granulocytic series. Although the increase in the total leukocyte count was not significant when all the cases were evaluated together, still the increase in the granulocytic series was prominent in the responders.

Because amifostine primarily effects the neutrophilic series, amifostine treatment may increase the risk of leukemic transformation in MDS-RAEB and MDS-RAEB-t patients who already have an increased risk of leukemia. However, no such transformation has been reported in the literature or observed in our study.

Another finding of our study was the manifestation of the therapeutic response only in MDS-RA (n= 1) and MDS-RARS (n= 2) cases. No MDS-RAEB case responded to the treatment. Considering these results, it would be appropriate to conclude that the drug should be administered in a selected group of patients with MDS-RA and MDS-RARS.

There are also some reports in the literature about the drug being ineffective. In some studies, amifostine is reported to be totally ineffective in MDS cases[11,26]. The question why the drug is effective in some and not in others is yet to be answered. It is speculated that this difference might be related to the dosage of the drug. But even when there was no difference in the dosage, differences were still observed in individual responses to therapy. Since the doses used in various studies differed and the therapeutic response was heterogenous, an optimal effective dose could not be determined yet. The fact that studies with amifostine were conducted in heterogeneous MDS subgroups that were also inadequate in regard to the total number of cases involved, also makes the evaluation of the drug's effectiveness more difficult. Moreover, the results of amifostine therapy can not easily be compare because of the differences between the criteria for the response of the treatment in literature.

In our study, the cytogenetic profile of the patients were unavailable. Therefore it could not be determined whether this factor also contributed to the therapeutic response of the patients. In the literature there are not enough studies to resolve this issue of whether cytogenetics modifies reponse to treatment or not.

Another important point that our study demonstrated was the duration of the drug's effect. Amifostine was effective only as long as it was being employed and its positive effects deteriorated quickly once the therapy was stopped. This fact presents a problem of cost effectiveness.

As a conclusion we can say that amifostine is effective in some MDS-RA and RARS cases. It is tolerated well and causes no major adverse effects. Since amifostine therapy needs to be prescribed for a long period of time and because of its high cost, we think it would be appropriate to administer the drug only to a group of highly selected patients.

In order to evaluate the efficacy of amifostine in the treatment of MDS more conclusively, more studies have to conducted. These should preferably be prospective randomized studies where different doses of amifostine are administered to an adequate number of patients including homogeneous groups of patients with MDS subgroups.

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