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The effect of ifosfamide and mesna in the treatment of children with various types of cancer

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Abstract

Background: Given that various types of cancer are major causes of death among children and there is no comprehensive study investigating the simultaneous effect of ifosfamide and mesna in the treatment of patients with various types of cancer in our country, this study aimed to assess the effect of ifosfamide and mesna in the treatment of children with various types of cancer.

Materials and Methods: In the retrospective study, 46 patients with cancer were divided into two groups. In the first group, patients were treated with ifosfamide (800 mg-1g/m2/day) with 500 cc of normal saline and mesna (equivalent to the amount of ifosfamide) in the serum. In the second group, the patient received ifosfamide through serum and mesna at 0, 4, 8, and 16 hours after the ifosfamide injection. This injection continued for three days. Then blood count, hemoglobin, and kidney tests in both groups were examined.

Results: White blood cells in both methods decreased significantly ($P<0.01$). In the second group, there was a significant difference before and after intervention, regarding hemoglobin level ($P<0.01$). In addition, more people in the second group showed gastrointestinal complications ($P<0.01$). There was no significant difference before and after intervention in the the two groups, regarding creatinine and urea levels ($P>0.05$).

Conclusion: In both groups, a decrease in white blood cells was observed, while kidney toxicity was not observed in any group. The decrease in hemoglobin in the second group was more than in the first group.

Keywords: Cancer, Ifosfamide, Mesna.

Introduction

Ifosfamide is a synthetic analog of cyclophosphamide and is used for treating various solid cancers (1). On the other hand, it is an antineoplastic and cytotoxic medicine used to treat and manage diverse cancers, including sarcoma, lymphoma, lung cancer (2), soft tissue, and bone sarcomas (3). It is considered a bi-functional alkylating agent and metabolized by the P450 cytochrome (CYP450) system to active components. These active metabolites, including acrolein and ifosfamide mustard (3), inhibit DNA synthesis (2). There are two mechanisms for the action of these metabolites. First: their actin causes damage to cells by forming intrastrand or interstrand crosslinks, leading to damaged cell apoptosis.

Second, the active metabolites up-regulate the reactive oxygen species, leading to irreparable DNA damage and protein formation stop (2). Moreover, ifosfamide is one of the active drugs in advanced sarcoma. It is applied as a single agent or as the first-line therapy with doxorubicin in patients who relapse after anthracycline-based chemotherapy. The toxicity of the central nervous system (CNS) of ifosfamide is revealed in some studies (4). Moreover, ifosfamide can induce nephrotoxicity; however, this mechanism may be related to oxidative damage. Taking antioxidants can effectively prevent ifosfamide's toxicity (5). Mesna or 2-mercaptoethane sulfonate Na is a synthetic compound with sulfhydryl groups used to prevent and decrease the hemorrhagic cystitis toxicity caused by

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acrolein. The efficacy of mesna in reducing ifosfamide kidney injury is unclear (5). Studies have shown that continuous infusion of ifosfamide and mesna without additional hydration is a choice in patients who take ifosfamide with hydration and mesna (6).

Although pediatric cancer is rare (7-12), it is one of the major causes of death among children (7). No comprehensive study investigated the simultaneous effect of ifosfamide and mesna in treating patients with various types of cancer; this study aimed to assess the effect of ifosfamide and mesna in the treatment of children with various types of cancer.

Materials and Methods

Sample selection

This retrospective study was conducted on children with leukemia and solid tumors referred to the pediatric oncology department of Shahid Sadoughi hospital. Inclusion criteria were all children with cancer under 14 years of age who were hospitalized and underwent chemotherapy in Shahid Sadoughi Hospital in 2019. Moreover, other inclusion criteria included no history of kidney disease or other metabolic diseases. If the patients needed an alternative treatment method or intended to withdraw, we excluded them.

Procedure

This study were included 46 patients. These patients were randomly divided into two groups. The first group (n=26 patients) was treated with ifosfamide (800 mg- 1 g/m^2/day) with 500 CC of normal saline, and the amount of mesna (which was equivalent to the amount of ifosfamide) was added to the serum. Ifosfamide and mesna were prepared the same way as before in the second group. Patients in the second group (n=16 patients) received ifosfamide injection and then mesna at 0, 4, 8, and 16 hours after ifosfamide injection. This injection continued for three days. Then blood count, hemoglobin, and kidney tests in both groups were examined.

Blood cell assay

Blood tests were taken from all the children before and ten days after the intervention to evaluate the blood cells.

Kidney toxicity assay

Creatine and urea factors were evaluated in both groups using the Pars Azmoon kit according to the manufacturer protocol, and the difference between these factors was also calculated.

Ethical consideration

After obtaining written consent from patients, the current study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.MEDICINE.REC.1398.261).

Statistical analysis

Data were entered into SPSS version 19. Chi-Square test, T-test, and Wilcoxon Signed Ranks Test were used for the analysis of data. $P<0.05$ was assumed to be significant.

Results

In this study, patients with leukemia and solid tumors referred to Shahid Sadoughi hospital were assessed, and 46 eligible patients were selected. Among them, four patients were excluded from the study. There were 26 patients in the first group (receiving ifosfamide and mesna simultaneously) and 16 in the second group (receiving ifosfamide and mesna hourly). The comparison of the two groups in terms of demographic data, including age and gender, is shown in Table I. According to the findings of Table I, there was no significant difference between the two groups in terms of demographic characteristics ($P>0.05$). The freqency of the two groups of patients regarding the the type of disease is shown in Table II.

The mean blood and biochemical parametes in the two groups is shown in Table III. As shown in Table III, white blood cells decreased in both groups, and there was significant difference before and after intervention regarding WBC ($P<0.05$). The mean platelet level showed a slight decrease in both treatment groups.

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In the first and second groups, severe reduction of platelets was observed in 3 and 4 patients, respectively, but no significant difference was seen before and after intervention(P>0.05). Moreover, the mean hemoglobin level in the first group slightly changed, but in the second group, the patients' hemoglobin decreased significantly (P<0.01). Moreover, there was no significant difference in the first and second groups before and after intervention regarding serum creatinine and urea levels (P>0.05). Moreover, 85% of patients in the second group showed digestive symptoms, while in the first group, only 17% demonstrated digestive complications; a significant difference was observed between the two groups (p =0.000).

Table I: Comparison of the two groups in terms of demographic data

Demographic data	The first group (n=26)	The second group (n=16)	P-value
Age (years)	5.16±3.21	5.40±4.0	0.291
Gender Boy Girl	 16 (61.5%) 10 (38.5%)	 10 (62.5%) 6 (37.5%)	 0.95

Table II: The frequency of the two groups of patients regarding type of disease

Disease	Total	The first group	The second group
Leukemia	18 (42.9)	11 (42.31)	7 (43.75)
Solid tumor	24 (57.10)	15 (57.69)	9 (56.25)
Total	42 (100)	26 (100)	16 (100)

Table III: The mean blood and biochemical parametes in the two groups

Group	WBC (Wbcs per microliter)	HB (g/dL)	Plt (×1000)	Urea (mg/dL)	Creatinine (mg/dL)
B.1	6821.74±5182.3	10.73±1.8	368.48±147.9	23.64 ±9.85	0.58±0.15
A.1	4915.50±3531.8	10.58±1.95	346.96±128.34	25.36±12.3	0.6±0.16
p-value	0.006	0.447	0.523	0.919	0.68
B.2	6873.3±3787.2	11.22±1.5	343.07±196	26.2±13.48	0.66±0.16
A.2	4531.25±2331.44	9.98±1.73	279.13±203.47	17.50±5.20	0.52±0.16
p-value	0.004	0.006	0.100	0.109	0.10

B:Before; A: after

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Discussion

In the current study, there was no significant difference before and after intervention in the first and second groups regarding the level of serum creatinine and urea. Coriat et al. assessed the efficacy of ifosfamide+mesna (as 1:1 concentration) over five days every three weeks for treating patients with sarcoma. They reported no acute encephalopathy or aggravation of kidney function (6). Schoenike et al., revealed that concurrent mesna and ifosfamide's adverse effects are urinary tract infection and renal toxicity (13). Skinner et al., revealed that chloroacetaldehyde is a major metabolite of ifosfamide which may be partly responsible for kidney toxicity. Although mesna may be able to detoxify the toxic metabolites, renal tubule delivery may not be enough to protect tubular glutathione from depletion by the metabolite that does not lead to preventing nephrotoxicity (14). Javad et al., reported that acute kidney injury due to ifosfamide could lead to chronic kidney disease. They also mentioned that mesna is not efficient for the prevention of this nephrotoxicity, and components, including N-acetylcysteine, may be impressive in the prevention of this nephrotoxicity (15).

Eliyas et al., evaluated the effect of ifosfamide (7500 mg/m2), doxorubicin (60 mg/m2), and dacarbazine (900 mg/m2) in patients with metastatic or unresectable sarcoma. Mesna was given for 84 to 96 hours at a dose of 2,500 mg/m2/d, and the findings showed severe mucositis, renal failure, and central nervous system toxicity in less than 5% of cycles (16). Arayju et al., evaluated the effect of ifosfamide and mesna in treating advanced squamous cell and neck cancer in 28 patients. Their findings showed no renal toxicity (17), but thrombopenia was observed in 1 case.

In addition, in the current study, white blood cells decreased in both groups, and their difference was significant. In the first group, five children who underwent treatment had a severe decrease in white blood cells, and in the children treated with the second method, there was a severe decrease in white blood cells in 3 patients (both approaches had the same effect). The mean platelet level decreased slightly in both treatment groups. In the first and second groups, severe reduction of platelets was observed in 3 and 4 patients, respectively. Moreover, the mean hemoglobin level in the first group slightly changed, but in the second group, the patients' hemoglobin level was more decreased. Alexa et al. assessed the effect of continuous infusion and bolus administration of ifosfamide and mesna in 10 children with Ewing sarcoma. In this regard, 48 and 24 cycles of ifosfamide as bolus administration and continuous infusion were administered. Patients who took this medicine had lower hemoglobin levels and platelet, leading to more transfusions and delayed treatment than continuous infusion. Therefore, continuous infusion of ifosfamide seems safe, but it should be confirmed in a larger population (18). Piura et al., assessed the effect of doxorubicin (30 mg/m2), ifosfamide (2000 mg/m2), and mesna (W/W 60%) in uterine sarcomas on days 1, 2 and 3 of every 21 days and thrombocytopenia was seen in 20% of patients. Moreover, anemia is seen in 20 % of patients (19). Crotzer et al. evaluated the effect of cisplatin, ifosfamide, and mesna in 9 patients with malignant mesodermal tumors of the ovary. They observed thrombocytopenia and anemia in 1 and 4 patients, respectively (20).

Bernstein et al. also revealed that ifosfamide with mesna demonstrated hopeful activity in children with multiple relapsed acute leukemia (21). Zidar et al. evaluated the effect of ifosfamide and mesna on diffuse malignant mesothelioma and treated patients (ifosfamide, 2 g/m2 intravenously for four days, and mesna 2 g/m2 intravenously for five days, every three weeks) and observed that 8% of

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patients achieved a partial response. Therefore, according to these findings, ifosfamide/mesna in treating malignant mesothelioma has modest activity. It can be evaluated using alternate dosage schedules and with other agents (22).

Kathryn et al., compared the outcome of soft tissue sarcoma treated with olaratumab and doxorubicin (group 1) versus doxorubicin, ifosfamide, and mesna (group 2) and observed that there was no significant difference between the groups regarding progression-free survival and overall survival. The difference between Kathryn and our studies was that we did not assess the survival of patients (23).

Conclusion

In both groups, a decrease in blood cells was observed, while kidney toxicity was not observed in any group. The decrease in hemoglobin in the second group was more than in the first group. In addition, a significant difference was seen between the two groups regarding digestive complications.

Conflict of interest

The authors declare no conflict of interest.

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