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Outpatient administration of Ifosfamide-Etoposide in a Cohort of Pediatric Sarcoma Patients: A Single Cancer Center Experience in Jordan

Sameer Yaser[1*], Iyad Sultan[2], Hadeel Halalsheh[2], Omar M. Albtoush[3], Jaafar Jaffal[5], Ahmad Shehadeh[6], Samer Abdelal[6], Omar Jaber[7], Wafaa Asha[8], Ramiz Abu Hijlih[8], Sereen Iweir[9], Nedal Al-Rawashdeh[9]

Abstract

The standard Ifosfamide-Etoposide (IE) regimen is typically administered in an inpatient setting. This study aimed to report our experience using outpatient administration in terms of safety and the potentiality of cost-reduction. A retrospective chart review was conducted for all pediatric patients diagnosed with any primitive neuroectodermal tumor (PNET) who had received outpatient Ifosfamide-Etoposide chemotherapy at KHCC in Jordan between 2007 and 2014. We evaluated the associated toxicity resulting from their treatment and compared the average treatment cost of the selected cases to the average cost of treatment for a comparable group of patients who received IE inside the hospital. Forty-eight patients were included, Forty-six were Ewing's sarcoma, and two patients were Rhabdomyosarcoma. Their toxicity profile revealed an overall tolerable profile; only three patients presented with hemorrhagic cystitis, and no toxic deaths were reported. The most common side-effect was grade 3-4 neutropenia (54% of the patients demonstrated it). Compliance with the urinalysis testing was found to be relatively low; 12% were submitted on time. Treatment cost for outpatients was found to be significantly less than it was for inpatient regimen, with a mean difference of 802.6 JOD (1132 USD) per cycle of Ifosfamide-Etoposide (P <0.001). The Outpatient Ifosfamide administration appears to be feasible and safe. It had a significant impact on cutting the cost. A structured prospective study is needed to confirm these findings. More focus is required on outpatient IE administration's effect on the quality of life and the methods to optimize adherence to study protocol, particularly in urinalysis testing.

Keywords: Ewing's sarcoma; Rhabdomyosarcoma; Ifosfamide; Etoposide; Outpatient treatment; Pediatric oncology

List of Abbreviations: IE: Ifosfamide-etoposide; PNET: Primitive Neuroectodermal Tumors; EFT: Ewing's family tumors; VDCA: Vincristine, doxorubicin, cyclophosphamide, and Actinomycin-D; KHCC: King Hussein Cancer Center; IRB: Institutional Review Board; ER: Emergency Room; TE: Toxic Event; ICU: Intensive Care Unit; GI: Gastrointestinal; ES: Ewing's Sarcoma; RMS: Rhabdomyosarcoma; Hrs.: Hours; STD: Standard Deviation; CI: Confidence Interval

Background

Ewing's family tumors (EFT) and Rhabdomyosarcoma are two examples of highly aggressive malignancies that are grouped as 'round blue-cell tumors' due to their characteristic cell morphology when histological stains are

Affiliation:

[1]Department of Medical oncology, King Hussein Cancer Center, Amman, Jordan

[2]Department of Pediatric oncology, King Hussein Cancer Center, Amman, Jordan

[3]Diagnostic Radiology Department, King Hussein Cancer Center, Amman, Jordan

[4]Department of Internal medicine, King Hussein Cancer Center, Amman, Jordan

[5]Department of Nursing, King Hussein Cancer Center, Amman, Jordan

[6]Department of Surgery, King Hussein Cancer Center, Amman, Jordan

[7]Department of Pathology & Laboratory Medicine, King Hussein Cancer Center, Amman, Jordan

[8]Department of Radiation Oncology, King Hussein Cancer Center, Amman, Jordan

[9]Office of Scientific Affairs and Research-Center of Research Shared Resources, King Hussein Cancer Center, Amman, Jordan

***Corresponding Author**
Sameer Yaser, Department of Medical oncology, King Hussein Cancer Center, Amman, Jordan.

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applied [1]. EFT is a systemic disease that causes subclinical metastasis for most of the patients. About 80-90% of patients undergoing local control (alone) develop relapse [2,3]. Treatment with Ifosfamide (With or without Etoposide); produced remarkable responses in patients who had a relapse after standard therapy for Ewing's sarcoma [4]. The addition of intensive multi-agent chemotherapy to local treatment has shown a remarkable impact on survival, with a reported 5- and 10-year survival rates being approximately 70 and 50 percent, respectively [3,5].

In metastatic disease treated by multimodality therapy, the long-term survival rates are lower than those for patients with localized disease [6].

The efforts of several cooperative groups lead to the evolvement of chemotherapy treatment for localized and advanced EFT. Previous studies have demonstrated the activity of Ifosfamide alone or in combination with Etoposide in patients with the relapsed disease [7,8].

In a randomized phase III clinical trial (the IESS-III study); for instance, the addition of IE to Vincristine, doxorubicin, cyclophosphamide, and Actinomycin-D (VDCA) was associated with significantly better five-year relapse-free survival compared with VDCA alone (69 versus 54 percent, respectively) in patients with localized disease but not in those with metastatic EFT or Primitive Neuroectodermal Tumors (PNET) [4]. This approach became the current standard in the United States. The described IE regimen initially requires hospitalization for intravenous administration of Ifosfamide; 1800 mg per square meter per day for five days (usually given with Mesna), and Etoposide 100 mg per square meter per day for five days [4,9].

When treating Ewing sarcoma with ifosfamide, toxicity is a challenging problem [10,11]. Therefore, it is recommended that administration occur under close supervision, which usually requires patient admission to the hospital [12].

In a busy specialized cancer center, bed availability is a significant impediment to delivering multiple chemotherapy cycles on time, bearing in mind the importance of maintaining dose density and intensity of chemotherapy. Accordingly, the outpatient-chemotherapy regimen of ifosfamide and etoposide can be more practical and more convenient to the patient. In this study, we are reporting our experience in using outpatient administration of IE in terms of safety and the potentiality of cost-reduction.

Materials and Methods

Study design

A retrospective chart review was conducted between 2007-2014 at King Hussein Cancer Center (KHCC) in Amman, Jordan. The medical charts of all pediatric patients diagnosed with any type of primitive neuroectodermal tumor (PNET), who received Ifosfamide-Etoposide (IE) treatment regimen in the outpatient setting were reviewed. Demographic data and data related to ifosfamide adverse events were collected and descriptive analysis were applied to report toxic related events.

To assess the difference in cost between receiving the treatment regimen while being inpatient versus outpatient; we extracted the study patients' billing records and compared it with the patients who received inpatient IE treatment during the same period. Cost of procedures that are not related to treatment administration were excluded.

The study was approved by and conducted in accordance with the guidelines of the Institutional Review Board (IRB) at KHCC.

The outpatient ifosfamide treatment protocol

The protocol for administration of IE to outpatient PNET cases at KHCC was as follows: Pre-chemotherapy hydration for 9 hours consisted of dextrose half-normal saline 160 ml/ m^2/hour (a maximum of 2000 mL/day), mixed with Mesna at 3 g/ m^2. The antiemetic regimen included Ondansetron at 0.5 mg/kg (maximum 8 mg IV every 8 hours. Dexamethasone 8 mg/ m^2 IV, Metoclopramide 0.5 mg/kg IV/PO every 6 hours PRN and Diphenhydramine 1.5 mg/kg (a maximum of 50 mg per dose).

The chemotherapeutic agents included are Etoposide at 100 mg/ m^2 IV over 1 hour, followed by Mesna infusion of 1 g/ m^2 for over 15 minutes, followed by Ifosfamide 1.8 g/ m^2 IV infusion for 3 hours followed by Mesna 1 g/m^2 IV over 15 minutes. The cycle was repeated every 21 days for a maximum of 9 cycles per patient.

At each IE cycle, patients underwent chemistry and hematology lab testing to monitor drug tolerance. Gastrointestinal and neurologic events post each IE cycle were also recorded by the hospital staff. Urinalysis was to be performed twice daily for each day of IE infusion.

Evaluation of safety

The case reports, admission charts, hematology, chemistry lab results, and emergency room (ER) visits of each patient post each outpatient-IE treatment cycle were obtained from the hospital archives and reviewed. Any reports of related adverse events were then flagged and categorized. Reported toxic events (TEs) were sorted into four categories: urology, hematologic, neurotoxic, gastrointestinal (GI) toxicities. Urology-related TEs referred to reports of microscopic hemoglobinuria, hemoglobinuria, gross hematuria, and hemorrhagic cystitis. Hematologic TEs included grades 3-4 neutropenia, neutropenic fever, intensive care unit (ICU) admissions, and grade 3-4 thrombocytopenia. Neurotoxic TEs include any reports of brain-involving adverse events,

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such as disorientation and seizures, while GI TEs consisted of grade 3-4 vomiting. The percentage of patients exhibiting signs of toxicity that fell into each of the four categories was calculated.

Comparison of the treatment cost

The cost of treatment for every cycle in the regimen of pediatric patients receiving outpatient IE treatment was collected from the finance department. To compare assess the difference in cost, we extracted the cost of treatment for every cycle in the regimen for all pediatric inpatient Ewing's sarcoma (ES) and rhabdomyosarcoma (RMS) cases that were admitted to KHCC during the same period (2007-2014), in order to reduce the effect of possible price inflation over time. At KHCC, the treatment regimen for PNET inpatients is identical to the outpatient regimen, with the exception of the addition of 24 hours hydration and the hospital stay for the inpatients.

The medical billing records for all patients in both groups were obtained to extrapolate the charges applied to patients from the start of their IE therapy to the last day all IE cycles. Charges related to chemotherapy administration, hospital bed occupation, nursing, lab tests, and management of IE-associated adverse events were included.

Statistical Analysis

Descriptive data analysis was used to report toxic events related to IE, and it was reported as numbers and percentages. An independent t-test was used to compare the mean cost of IE administered as outpatient versus the mean cost for inpatient comparator. Statistical significance was defined as P-value <.0.05. Data analysis was carried out using the Statistical Package for Social Sciences (SPSS) program version 26 for Mac (IBM Corp., Armonk, USA).

Results

Forty-eight pediatric patients received the out-patient IE protocol. Their ages ranged between two and 17 years old (median age: 11 years), and 62.5% were males. Of the outpatient cases reviewed; 46 were bone-ES and 2 patients were treated for RMS. Eleven (22.9%) of PNET patients presented with metastatic disease, with the lungs being the primary site of metastasis (n=9, 18.8% of the outpatients), while 37 had localized tumors. A summary of the general characteristics of the PNET outpatients, as well as those for the inpatient control group, can be found in Table 1.

Forty-three patients (90%) continued the protocol as outpatients, while only five patients required inpatient

Table 1: Demographical characteristics of the PNET outpatients included in this study and for the inpatient group that was used as a control group in the treatment cost analysis.

Characteristic	Outpatients	%	Inpatients	%	Total	%
Number of patients	**48**		**27**		**75**	
Age (Range: 2-17 years old)	**Median: 11.3**		**Median: 12.9**			
<6	8	16.7	6	22.2	14	18.7
6-11	13	27.1	4	14.8	17	22.7
12-17	27	56.3	15	55.6	42	56.0
Gender						
Male	30	62.5	14	51.9	44	58.7
Female	18	39.6	13	48.1	32	42.7
Diagnosis						
ES	46	95.8	24	88.9	70	93.3
RMS	2	4.2	3	11.1	5	6.7
Tumor site						
Bone	45	93.8	22	81.5	67	89.3
Soft tissue	3	6.3	5	18.5	8	10.7
Metastatic disease						
Yes	11	22.9	7	25.9	18	24.0
No	37	77.1	20	74.1	57	76.0
Site of Metastasis						
Lung	6	12.5	3	11.1	9	12.0
Lung and bone	2	4.2	2	7.4	4	5.3
Lung and bone marrow	1	2.1	0		1	1.3
Others*	2	4.2	2	7.4	4	5.3

ES= Ewing's sarcoma, RMS= rhabdomyosarcoma.
**Others includes cases of patients who were diagnosed with Lung and heart metastasis, and Lung, bone and peritoneum metastasis*

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admission at some point to continue treatment. Moreover, 7 patients had blood hemoglobin drop below 8 g/dL and consequently needed blood transfusion. According to the logs for the provided chemotherapy, a total of 249 cycles of IE were dispensed to the 48 patients; the number of cycles given ranged from one to nine cycles, with an average of five IE cycles administered to each patient (Table 2).

Reported toxicity

The observed number of toxicities post all IE cycles (249 cycles) given to the 48 patients and the percentage of each type of toxic event per cycle are summarized in Table 2 and Figure 1. The information obtained from the charts of the ES and RMS patients included in this study revealed that there were no observed deaths due to IE toxicity and that out of all administered IE doses (i.e. the 249 cycles); only three hemorrhagic cystitis events were recorded. Moreover, there were only three instances in which the patients required ICU admission and three reports of neurotoxic events. None of the patients presented with gastrointestinal TEs.

The majority of the reported TEs consisted of hematologic toxicities, with grade 3-4 neutropenia being the most commonly reported event (44.7% of all reported TEs). It happened post 59% of all IE cycles. The percentage of febrile neutropenia and thrombocytopenia were 14.3% and 11.5% respectively. A total of 322 TEs were reported, with the majority (n=169) occurring during the first three cycles of IE treatment (Table 2). No toxicities were reported post-cycle 7.

Table 2: List and percentages of reported adverse events (n = 322) post outpatient administration of each ifosfamide/etoposide (IE) cycle.

Number of IE Cycle	C1	C2	C3	C4	C5	C6	C7	C8	C9		
No. of patients who completed each cycle	48	43	38	34	28	26	23	22	1		
Type of TE										Total no. of TEs	%
Neurologic	0	0	1	1	0	0	1	0	0	3	0.9
Gross Hematuria	2	0	0	0	0	0	0	0	0	2	0.6
Hemorrhagic cystitis	0	0	0	0	0	1	0	0	0	1	0.3
Hemoglobinuria	17	10	7	6	5	6	4	0	0	55	17.1
Microscopic- hemoglobinuria	10	3	4	6	2	2	2	0	0	29	9.0
Grade 3-4 vomiting	1	0	0	0	0	1	0	0	0	2	0.6
ICU visit due to toxicity	0	0	1	1	0	1	0	0	0	3	0.9
Thrombocytopenia	5	7	5	4	6	6	4	0	0	37	11.5
Febrile neutropenia	7	11	9	5	7	2	5	0	0	46	14.3
Grade 3-4 neutropenia	23	23	23	22	20	16	17	0	0	144	44.7
Total no. of TEs	65	54	50	45	40	35	33	0	0	322	100

TEs=Toxic Events, C= Cycle

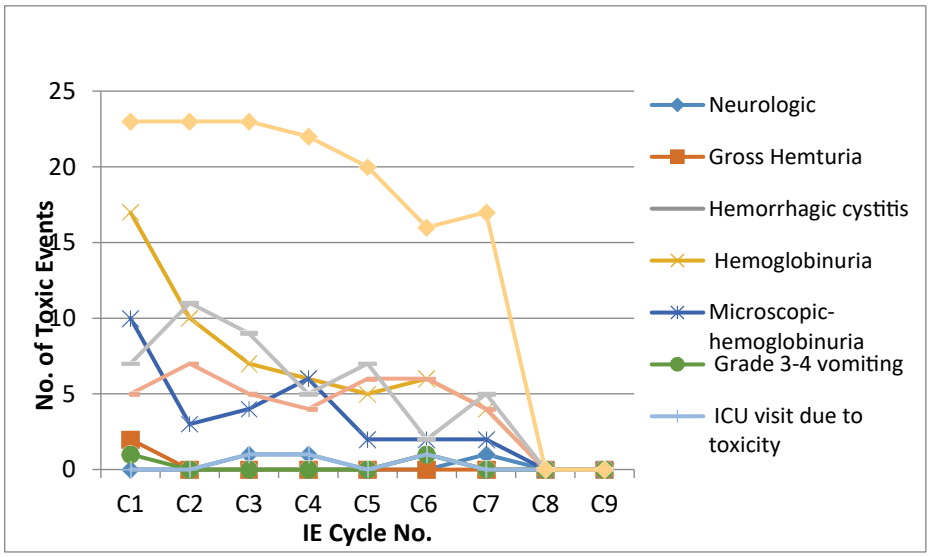

Figure 1: Distribution and type of total recorded toxic events that occurred after each cycle of Ifosfamide/etoposide (IE) administered in an outpatient setting.

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Compliance with urinalysis testing was low; however, only 12% of the required samples were received on time (i.e., within 1 h of urine collection), and 54% of the patient-charts were devoid of any urinalysis testing results (Figure 2). The data that was available, nonetheless, revealed that hemoglobinuria was reported after 55 of the IE cycles, amounting to 17.1% of the reported TEs, while microscopic-hemoglobinuria and gross-hematuria were reported in 9.0% and 0.6% respectively (Table 2).

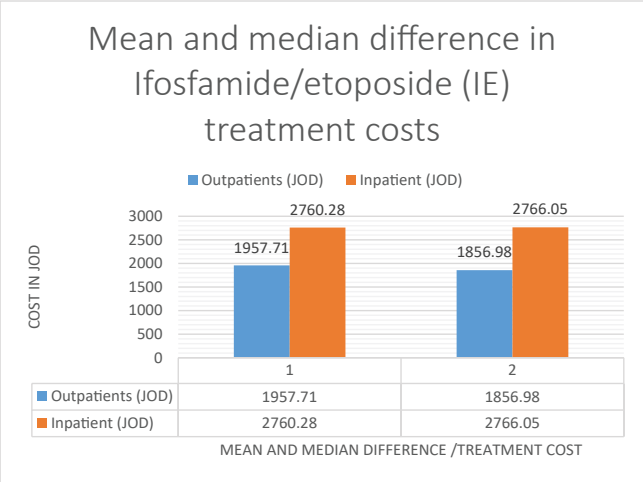

Figure 2: Mean and median difference in Ifosfamide/etoposide (IE) treatment costs.

The difference in treatment fees

After reviewing the billing records for the IE treatment-associated charges of the patients included in this study and excluding irrelevant or supplementary fees (e.g., instances of hip replacement, medications due to chronic illnesses… etc.), the mean cost ± STD of a single IE cycle was 1957.7 ± 648.3 JOD (approximately 2761.7 USD) for outpatients while the mean cost ± STD for the matched cases comprising the inpatient cohort was found to be 2,760.3 ± 1335.9 JOD (3893.3 USD) per admission for each IE treatment cycle. The difference in cost per cycle was found to be statistically significant, with a mean difference of 802.6 JOD (1132 USD) per cycle (P <.001, 95% CI: 470.48-1134.65) (Table 3). Since; on average, each patient received five cycles of IE, this amounts to an average 4013 JOD (5660.2 USD) reduction in treatment cost per patient and a potential total decrease in treatment fees of about 192624 JOD (271687.5 USD) for all the 48 outpatients.

Table 3: Mean and median difference in Ifosfamide/etoposide (IE) treatment costs between pediatric inpatients and outpatients.

Patient Group	Mean	Median	*P*-value
Total cost of each IE cycle given to outpatients (JOD)	1957.71±648.3 JOD	1856.98 JOD	<0.001*
Cost of stay for each inpatient visit for IE administration (JOD)	2760.28±1335.9 JOD	2766.05 JOD	

*JOD= Jordanian Dinar, SD= Standard deviation, CI= confidence interval. *indicates statistical significance*

Discussion

This study provides an ample evidence that not only is the safety of outpatient IE therapy comparable to its inpatient counterpart, but it is also more affordable for the patient and cost-effective for the hospital. This offers an important avenue for the application of chemotherapy for pediatric patients in outpatient settings, further easing what is already a taxing process on the patient's quality of life and presenting hospitals with attractive financial incentives.

This report which is a single cancer institution experience is the first study from the region to elude on the applicability of out-patient administration of IE. One report came from western Saudi Arabia on pathological characterization of ES sarcoma without any management details [13]. Previous studies have established the safety of outpatient administration of modified IE protocol [13,14].

It is evident that the main concern with Ifosfamide is renal impairment and hemorrhagic cystitis, which tends to be markedly reduced by the administration of Mesna and inpatient 24 hours super-hydration [15]. In this study; it is remarkable that out of 249 cycles of IE (with Mesna), only three cases were reported with hemorrhagic cystitis/gross hematuria. This rate is consistent with the rates reported in previous trials [16]. The same applies for asymptomatic hemoglobinuria [16].

Furthermore, most of the side effects diminish after third cycle and becomes infrequent post-cycle 7.

The few instances of recorded neurotoxic events also paint a promising outlook on the safety of this method of treatment delivery, especially since neurotoxicity is a significant concern of ifosfamide treatment, particularly in pediatric patients [17]. The hematologic toxicities reported in this study, such as those of neutropenia and thrombocytopenia, are predictable outcomes of antineoplastic medications and fell into the expectations of inpatient IE related toxicities reported in the literature [9,13,18,19]. A study evaluating outpatient ifosfamide regimens for non-Hodgkin's and Hodgkin's lymphoma reported a similar trend in toxic side effects [20], as well as a study that evaluated outpatient ifosfamide therapy in pediatric soft-tissue cancer patients; finding a comparable toxicity profile in their outpatient and inpatient arms [13].

Over the past couple of decades, there has been a clear shift in healthcare systems' tendency to shift to outpatient or ambulatory services [21]. According to several studies, hospitalization has been determined to be a detrimental factor in the quality of life of patients receiving chemotherapy

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[22,23]. A study conducted by Vaughn et al. [24] reported on the overwhelming desire for acute myeloid leukemia patients to receive their treatment as outpatient, particularly while being in a pancytopenic state. In addition to the essential benefit of providing further comfort for patients, outpatient care has proven to be a source of increased revenue for hospitals; the Deloitte Center for Health Solutions analyzed hospital data between 2005 and 2015 and revealed that along with the 6.6% decline in hospital stays, gross revenue for hospitals from outpatient services grew 45% [25]. The demonstrated significant decrease in treatment fees for the patients who received outpatient IE treatment in this study (Table 3), provides a potential incentive for investment in the development of outpatient treatment protocols, particularly for pediatric and adult sarcoma patients, whose lower quality of life indices may be benefited by the ambulatory approach.

One of the challenges of outpatient treatment is the issue of patient compliance with testing. For the patient cases reviewed in this study, it was apparent that some of the patients did not follow the requirements of daily urine collection to assess urologic toxicity. Prospective studies on the outpatient administration of IE should employ stricter regulation for urine collection and/or provide further assistance to patients when collecting their urine samples.

We recognize the limitations in this study; being retrospective study, small cohort and lacking the quality of life data. The results of this report may establish the ground for prospective trials that may change our practice in future and modify the way we give IE protocol.

Conclusion

Outpatient Ifosfamide and Etoposide administration is feasible and reported toxic events do not differ from previously reported in an inpatient setting. On the other hand, outpatient administration of Ifosfamide significantly reduced the cost. This method of chemotherapy administration offers an important avenue for cancer patients, it reduces the cost of treatment and might help in reducing the burden on bed capacity at the hospital. Conducting similar studies as well as prospective ones on larger scale will help realize the goal of establishing a comprehensive standardized outpatient treatment protocol for ES and RMS.

Ethics approval and consent to participate

The study was approved by and conducted in accordance with the guidelines of the Institutional Review Board (IRB) at KHCC.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

The authors declare no competing financial interest conception or design of the work.

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