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Feasibility and safety of outpatient administration of ifosfamide and etoposide for pediatric patients with Ewing sarcoma in a resource-limited setting amid the COVID-19 pandemic

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Abstract

Background: To assess feasibility and safety of outpatient administration of ifosfamide and etoposide (IE) for pediatric Ewing sarcoma (EWS) patients in a resource-limited setting amid the COVID-19 pandemic.

Materials and Methods: Retrospective study of patients with EWS who received outpatient IE from January 2020 until January 2021 at our institution. Ifosfamide 1800 mg/m^2 was given for 5 days with MESNA (2-mercaptoethane sulfonate sodium) infusion and additional boluses before and after 9 hours of hydration. Patients >10 years of age with the ability to drink orally at home, no pre-existing renal dysfunction or history of hematuria were included. They were monitored for hemorrhagic cystitis with a urine dipstick before, midway, and at end of infusion. A urine analysis was done 24 hours after the last dose of ifosfamide.

Results: Forty-seven (100%) cycles were given as outpatient during the study period. Thirty-five (74%) cycles were given on time, two (4%) cycles were delayed due to mucositis, two (4%) due to delayed count recovery, and eight (18%) due to unavailability of outpatient appointments. The median interval between these cycles was 15 days (range 14–44 days). No episode of hemorrhagic cystitis was reported. Urine analysis was not done at 24 hours for 27 (58%) cycles, so microscopic hematuria may have been missed. This outpatient protocol saved 32% (USD 299) per cycle in cost and 282 days of hospitalization.

Conclusion: Outpatient administration of IE for pediatric patients with EWS is feasible, safe, and cost-effective during the COVID-19 pandemic.

KEYWORDS
COVID-19 pandemic, Ewing sarcoma, feasibility, ifosfamide, outpatient

Abbreviations: EFS, event-free survival; EWS, Ewing sarcoma; HIC, high-income countries; IE, ifosfamide and etoposide; LMIC, low middle-income countries; MESNA, 2-mercaptoethane sulfonate sodium.

1 | INTRODUCTION

Ewing sarcoma (EWS) is the second most common pediatric bone tumor. It is a highly aggressive cancer, with overall survival (OS) of 70% with nonmetastatic and ~30% with metastatic disease.[1,2] The treatment comprises neoadjuvant chemotherapy, followed by local control by surgery or radiotherapy.[3] The two weekly interval-compressed chemotherapy regimen of vincristine, doxorubicin, and cyclophosphamide (VDC) alternating with ifosfamide and etoposide (IE) is the standard of care for pediatric patients with EWS. The 5-year event-free survival (EFS) in pediatric patients of nonmetastatic EWS has been improved from 65% to 73% by the use of an interval-compressed chemotherapy regimen that requires timely administration after every 2 weeks.[4,5]

The COVID-19 pandemic presents a global challenge to safe and effective pediatric cancer care, especially in low middle-income countries (LMIC). Around 90% of the world's pediatric cancer population belongs to LMIC.[6] The challenge is to provide pediatric cancer care due to the potential risk of significant delay in treatment and limited medical services, especially in LMIC, like Pakistan.[7] Delays in cancer treatment can lead to tumor progression and poorer outcomes.[8] So, there is an urgent need for safe and feasible adaptations to cancer treatment.[6]

Ifosfamide is an alkylating agent and is activated by hepatic cytochrome P450 enzyme CYP3A4 into isophosphoramide mustard and toxic metabolite acrolein. Acrolein is associated with urothelial toxicity leading to hemorrhagic cystitis. This toxicity can be prevented by infusion of thiol compound 2-mercaptoethane sulfonate sodium (MESNA), followed by hyperhydration for 24 hours after ifosfamide administration.[3] MESNA provides uro-protection by binding with acrolein, preventing damage to bladder epithelium.[9] This requires inpatient admission for 6 days, and places a significant admission burden on hospitals, and causes delays in treatment when inpatient hospital beds are already limited, especially during the COVID-19 pandemic. So, an altered regimen needs to be followed to replace long treatment visits with shorter hospital visits.[10]

Elshahoubi et al.[2] and Maezza et al.[3] have demonstrated that IE can be administered in the outpatient setting without any increase in toxicity. However, no significant local data regarding the feasibility of outpatient administration of IE in pediatric EWS in a resource-limited country like Pakistan is available. So, based on previously published studies, an institutional protocol for safe outpatient administration of 1800 mg/m^2 of ifosfamide for 5 days with MESNA hydration was developed to reduce days of inpatient hospitalization and to ensure safe and timely administration of IE for pediatric patients with EWS. We conducted this study to assess the feasibility and safety of outpatient administration of IE for pediatric patients with EWS in a resource-limited setting amid the COVID -19 pandemic.

2 | METHODS

A retrospective review was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH&RC), Lahore, Pakistan. It was done after approval from the institutional review board of the hospital. The in-house electronic information system database was used to identify the diagnosed cases of pediatric EWS registered at SKMCH&RC, Lahore, Pakistan who received the interval-compressed IE chemotherapy in the outpatient setting from January 2020 to January 2021.

Protocol for safe outpatient administration of 1800 mg/m^2 of ifosfamide for 5 days was developed with MESNA bolus (600 mg/m^2) before the start of infusion and at end of 9 hours of hydration, as shown in (Figure 1) and evidenced by Meazza et al. where MESNA was given in the dose of 160% of total ifosfamide dose.

The patients with histologically proven EWS, older than 10 years of age with the ability to drink orally at home with no previous history of renal dysfunction or hematuria were selected for outpatient administration. The patients were daily monitored for hemorrhagic cystitis with a urine dipstick before, midway (3–4 hours), and at the end of post chemotherapy hydration (9 hours). Urine analysis was done 24 hours after the last dose of ifosfamide. On the sixth day, granulocyte colony-stimulating factor was started at a dose of 5 μg/kg/day subcutaneously until blood count recovery. The patients were instructed to visit the emergency department if they observed three or more episodes of vomiting or any change in the color of urine. They were admitted if persistent emesis or hematuria developed at any time.

2.1 | Data analysis

Data were analyzed using a Statistical Package for Social Sciences (SPSS) version 20. Age was presented as mean and standard deviation. Categorical data like the outcome in terms of the timely administration of chemotherapy, the incidence of hemorrhagic cystitis, reduction of cost of administration of chemotherapy, and reduction in days of hospitalization were presented as frequencies and percentages.

3 | RESULTS

In our study, a total of 20 patients were studied, the mean age was 13.9 ± 2.12 years. Twelve (60%) were males and eight (40%) were females. The male to female ratio was 1.5:1. Total 47 cycles were given as outpatient during the study period.

3.1 | Feasibility of administration

Thirty-five (74%) cycles were given on time, two (4%) cycles were delayed due to mucositis, two (4%) due to delayed count recovery, and eight (18%) due to lack of availability of outpatient appointments. The median interval between the chemotherapy cycles was 15 days (range 14–44 days). All 47 (100%) cycles were completed in the outpatient setting. No episode of hemorrhagic cystitis was documented by urine dipsticks, done thrice daily for 5 days (100%) and by urine

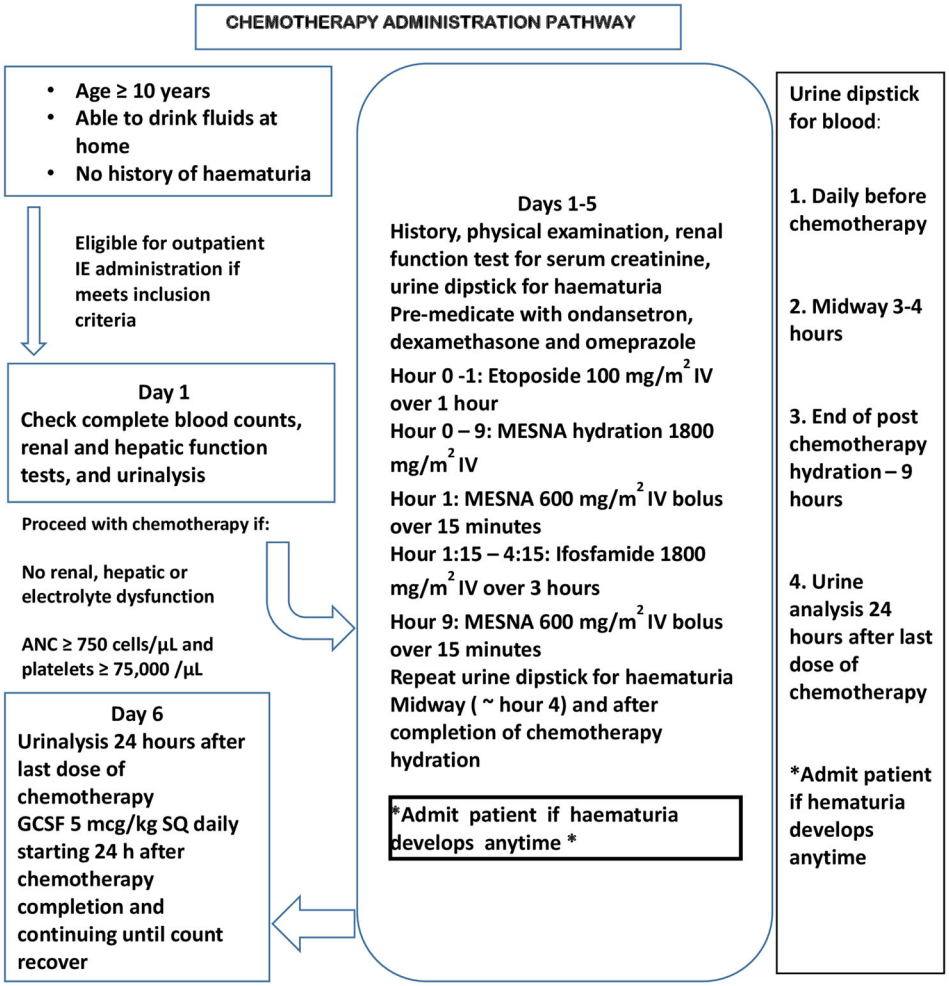

FIGURE 1 Pathway for safe outpatient administration of 1800 mg/m^2 ifosfamide with 9 hours of MESNA and hydration

analysis done 24 hours after the last dose of chemotherapy in 20 cycles (42%).

3.2 | Safety of administration

There were no documented episodes of hemorrhagic cystitis. Urine analysis was not done after 24 hours of the last dose of ifosfamide for 27 (58%) cycles, so microscopic hematuria may have been missed. However, none of the patients developed gross hematuria.

3.3 | Reduction in cost and bed occupancy

The cost of inpatient and outpatient IE chemotherapy administration per cycle was PKR 142,843 and PKR 96,989, respectively. It saved PKR 2,155,138 for 47 cycles (PKR 45,854 or USD 299/cycle) and 32% of the total cost of chemotherapy. Each inpatient IE cycle needed 6 days of hospitalization, so outpatient IE administration resulted in 282 fewer days of hospitalization during the study period.

4 | DISCUSSION

The protocol used in our study for safe outpatient administration of IE with MESNA hydration was based on previously mentioned studies of Elshahoubi et al.[2] and Maezza et al.[3] Both of these studies show results similar to our study. In the Elshahoubi et al. study, a total of 145 cycles were given in an outpatient setting. Fifty-nine percent of cycles were administered on time, compared with 74% of cycles in our study. The median interval between these cycles was 16 days. Two cycles (1.3%) were switched to inpatient; however, no cycle was switched to inpatient in our study. Acute ifosfamide toxicity was similar to our study. Microscopic and transient gross hematuria was reported in one cycle each, versus none in our study. It was cost-effective, as it saved 21% of the total cost of chemotherapy.[2] In the Meazza et al. study, out of 468 cycles of ifosfamide given as outpatient, hemorrhagic cystitis was reported in only three cycles (0.6%).[3] These studies showed that ifosfamide could be safely administered to outpatients, replacing the 24 hours prolonged MESNA hyperhydration with 9 hours long simplified hyperhydration. Thus, resulting in shorter hospital stays and consequently lower costs.[3]

The Children's Oncology Group (COG) study showed that the compressed chemotherapy regimen (AEWS0031) improved 5-year EFS in pediatric patients of nonmetastatic ESW from 65% to 73% in contrast to three weekly standard chemotherapy regimen. The prognosis was improved by timely two weekly interval-compressed chemotherapy, followed by granulocyte colony-stimulating factor for accelerated neutrophilic and platelet count recovery.[5] It required inpatient admission for 6 days after every 2 weeks and led to a significantly high admission burden on resource-limited countries. Delay in chemotherapy administration may lead to tumor progression and worse outcomes. It poses a dilemma for LMICs where health care resources are limited.

Pediatric cancer care has been considerably affected by the COVID-19 pandemic.[11] The major concern for cancer patients is the inability to receive necessary cancer treatment on time.[12] It has led to an increased burden on inpatient hospital beds and significant delays in cancer treatment, resulting in poorer disease outcomes and exhaustion of health care services.[10] Edge R showed that 42% of cancer patients and survivors reported some level of disruption to their cancer treatment.[11] The limited human and medical resources in the COVID-19 crisis emphasize the need for prioritization of beneficial treatments.[13] de Joode et al. reported that up to 30% of cancer patients had modifications in their treatment during the COVID-19 pandemic.[14] So, the cancer treatment needs to be delivered on time with safe and feasible adaptive measures.[12]

We observed that IE can be given with 100% success in the outpatient department in pediatric patients with EWS in a resource-limited setting and inpatient admissions can be averted and these beds can be saved for the COVID-19 patients.

Low-income and middle-income countries have predominantly large younger populations and fragile health care system.[15] Therefore, LMICs have a larger burden of cancer-related deaths than high-income countries (HICs).[16] In HICs, 80% of pediatric cancer patients are treated successfully.[17] In contrast, about 70% of cancer deaths occur in LMICs.[18] The survival for EWS in children in LMICs falls behind HICs due to the nonavailability of timely, effective, and affordable treatment.[19] The increase in cancer burden in LMICs poses a threat to already frail health care and economic infrastructure. Despite the availability of effective chemotherapy, cost-effectiveness is of utmost concern.[20] The two weekly interval-compressed inpatient chemotherapy regimen in pediatric patients with EWS places a significant burden on cancer care services in LMIC. So, this outpatient IE administration protocol can be used routinely in LMIC like Pakistan, where inpatient beds and medical finances are limited.

The limitation to our study was that it was a retrospective study conducted on a small number of patients. The analysis of the quality of life of patients who received IE as an outpatient and long-term toxicities of ifosfamide are the domains that need further exploration.

5 | CONCLUSION

Outpatient administration of IE for pediatric patients with EWS is feasible, safe, and cost-effective, with a reduction in the cost of chemotherapy and days of hospitalization. This was particularly useful in the timely administration of chemotherapy during the COVID-19 pandemic when inpatient beds were limited.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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