CASE SERIES

PATTERN OF CHEMOTHERAPY INDUCED TOXICITIES IN CHILDREN WITH EWING SARCOMA: A CASE SERIES

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Background: Ewing sarcoma is a rare and aggressive bone or soft tissue cancer that primarily affects children and adolescents. Estimated incidence of Ewing sarcoma is reported to be 1.2–2.9 in one million individuals in England and 1 in one million in the US. Objective of the study was to determine the pattern, and influence of gender and age on chemotherapy-induced toxicities in children with Ewing sarcoma. This descriptive case series was carried out at the Department of Paediatric Oncology, CMH Rawalpindi, from January 2014 to June 2023. **Methods:** Children of either gender aged less than 18 years and diagnosed cases of Ewing Sarcoma were enrolled. All patients were given VIDE (vincristine, ifosamide, doxorubicin, etoposide) chemotherapy and patients were observed for chemotherapy induced toxicities. Chi square test was used to analyze significance of age and gender on toxicity. **Results:** In a total of 59 children 35 (59.3%) were male and 24 (40.7%) females. Out of these 11 children expired. The mean age was 7.59±3.87 years. Younger age was strongly associated with higher occurrence of toxicity specifically children under 5 years being most affected (p<0.05). Neutropenia, nausea and vomiting, thrombocytopenia, and diarrhoea were the most frequent adverse events observed in 53 (89.9%), 37 (62.7%), 36 (61.0%), and 36 (61.0%) patients respectively. There was no association of gender with chemotherapy induced toxicity. Neutropenic sepsis and diarrhoea were positively associated with mortality in the 11 children who expired (p<0.05). **Conclusion:** Neutropenia, nausea and vomiting, mucositis, thrombocytopenia and diarrhoea were the most frequent chemotherapy induced toxicities in children with Ewing sarcoma. Younger children specifically under 5 years have a higher chance of chemotherapy induced toxicities however gender did not seem to influence related toxicities. Neutropenic sepsis was the major predictor of mortality warranting higher vigilance and aggressive management of infections.

Keywords: Ewing sarcoma; Antineoplastic combined chemotherapy protocols; Chemotherapy; Adverse effects; Neutropenia

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INTRODUCTION

Ewing sarcoma is a rare and aggressive bone or soft tissue cancer that primarily affects children and adolescents. Estimated incidence of Ewing sarcoma is reported to be 1.2–2.9 in one million individuals in England and 1 in one million in the US.[1] Ewing sarcoma originates from the neural crest cells as a result of chromosomal aberrations and consequent formation of EWS-FLI1 fusion gene which promotes oncogenesis in 85% cases of Ewing sarcoma.[2]

The treatment of Ewing sarcoma often involves a combination of surgery, radiation therapy, and chemotherapy.[3] While chemotherapy is an integral component of the treatment regimen, it is known to be associated with a range of toxicities that can significantly impact the well-being of young patients.[4] These toxicities can lead to treatment interruptions, compromised quality of life, and potential long-term health consequences.[5] Understanding the pattern of chemotherapy-induced toxicities specific to the Pakistani paediatric population with Ewing sarcoma is crucial for optimizing treatment protocols, improving patient outcomes, and enhancing the overall management of this aggressive malignancy. Limited studies have investigated the pattern of chemotherapy-induced toxicities in children with Ewing sarcoma, particularly within Pakistan. International studies have indicated that bone marrow suppression, including anaemia, neutropenia, and thrombocytopenia are frequently observed in paediatric Ewing sarcoma patients undergoing chemotherapy.[6] Nausea, vomiting, and gastrointestinal symptoms are also reported side effects. Hair loss (alopecia), fatigue, and increased susceptibility to infections have been observed across different paediatric cancer populations.[7]

Given the unique genetic, environmental, and healthcare factors in Pakistan, it is imperative to conduct

research that specifically addresses the Pakistani population. This research focused on determining the pattern, and influence of gender and age on chemotherapy-induced toxicities in children with Ewing sarcoma in Pakistan, addresses a critical gap in the literature. The impact of Ewing sarcoma on young patients and their families can be substantial due to its aggressive nature and potential long-term effects. The incidence or treatment outcomes of any type of cancer is not well documented in the country due to the lack of a cancer registry. This research will not only provide insights into the impact of chemotherapy on patients with Ewing sarcoma but will also guide the development of tailored supportive care strategies to mitigate toxicities and enhance treatment adherence. By investigating the specific toxicities experienced by these young patients within the Pakistani context, the study aims to contribute to the optimization of treatment protocols and the improvement of patient care. This research holds the potential to inform clinical practice and policy decisions related to paediatric Ewing sarcoma treatment in Pakistan, ultimately enhancing the quality of life and outcomes for affected children and their families.

MATERIAL AND METHODS

The study was a descriptive case series undertaken in the department of Paediatric Oncology, CMH, Rawalpindi, Pakistan, from January 2014 to June 2023. Approval from Institutional Ethical Committee was obtained. Informed and written consents were acquired from parents/guardians of all patients. Admitted children of either gender aged less than 18 years and known cases of Ewing sarcoma were analyzed. Parents or guardians of children who refused to be part of this study were excluded from this study. Non-probability consecutive sampling technique was adopted and all cases fulfilling the inclusion criteria were included. All patients were given VIDE (vincristin, ifosamide, doxorubicin, etoposide) chemotherapy before local control according to EURO EWING 2012 protocol.[8] Chemotherapy was given during the inpatient stay and patients were observed for chemotherapy induced toxicities and managed accordingly as per institutional protocols. The use of granulocyte-colony–stimulating factor (GCSF) was encouraged but was not mandatory. Neutropenia was labelled as absolute neutrophil count below 1.5 x 10^9/l. Thrombocytopenia was named when platelet count was below 150 x 10^9/l. Anaemia was labelled as haemoglobin below 10 g/dl.

Data was analyzed using SPSS-26.0. Nominal data were shown as frequency and percentages while quantitative data were given mean and standard deviation representation. Chi-square test was applied to compare data between various chemotherapy induced toxicities to identify any possible significant associations. *p*-value below 0.05 was taken as significant.

RESULTS

In a total of 59 children with Ewing sarcoma, there were 35 (59.3%) male and 24 (40.7%) female, representing a male to female ratio of 1.5:1. The mean age was 7.59±3.87 years, ranging between 3 months to 18 years. The details about the gender and age distribution are shown in table-1.

Table-1: Gender and Age Distribution of Children with Ewing Sarcoma (n=59)

Characteristics		Number (%)
Gender	Male	35 (59.3%)
	Female	24 (40.7%)
Age (years)	<5	15 (25.4%)
	5–12	37 (62.7%)
	13–18	7 (11.9%)

Evaluation about the chemotherapy induced toxicities revealed that neutropenia, nausea and vomiting, thrombocytopenia, and diarrhoea were the most frequent, noted in 53 (89.9%), 37 (62.7%), 36 (61.0%), and 36 (61.0%) patients respectively. The details about the frequency of chemotherapy related toxicities among children having Ewing sarcoma are shown in figure-1. There were 29 (49.2%) patients who reported administration of red cell concentrates. Granulocyte-Colony Stimulating Factor (GCSF) had been given in 34 (57.6%) patients.

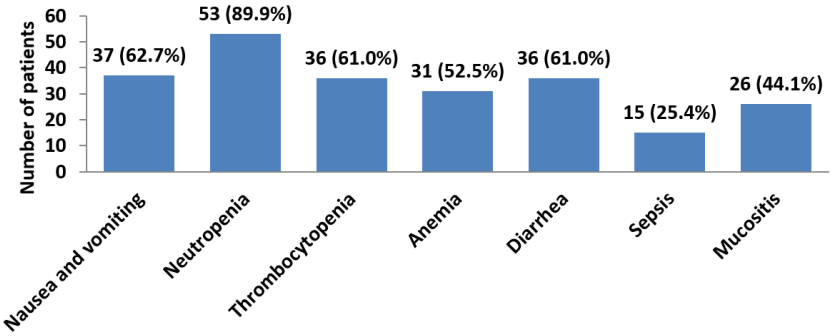

Figure-1: Frequency of chemotherapy induced toxicities in children with Ewing Sarcoma (n=59)

We observed that children below 5 years of age were adversely affected by chemotherapy related toxicity. It was found that Gastrointestinal related toxicities (nausea, vomiting, diarrhoea) were significantly more common in children aged below 5 years (p<0.05). Furthermore, anaemia and mucositis were also significantly associated with younger age as almost 80% of children under 5 years of age suffered from these toxicities (p<0.05). Although we found a larger number of children under 5 years of age suffering from thrombocytopenia and neutropenia but this was not found statistically significant in analysis. There were 12 (80.0%) children below 5 years of age who were administered red cell concentrates versus 14 (37.8%) between 5–12 years, and 3 (42.9%) between 13–18 years and the difference was found to be significant (p=0.021). There was no statistical difference in age and gender on the possibility of child having sepsis post chemotherapy. No significant association of gender with any of the chemotherapy induced toxicities was found (p>0.05). Comparison of gender and age with respect to various chemotherapy induced toxicities and tendencies towards red cell concentrates and GCSF administration are shown in table-2 and 3. Mortality was reported in 11 out of 59 patients (18.6%). Neutropenic sepsis was observed in all children who expired. (Diarrhoea (90.9% vs. 54.2%, p=0.024), as well as sepsis (100% vs. 8.3%, p<0.001) were found to have significant association with mortality (table-4).

Table-2: Stratification of gender and age with respect to chemotherapy induced toxicities (n=59)

Toxicities	Gender			Age (years)			
	Male (n=35)	Female (n=24)	*p*-value	<5 (n=15)	5-12 (n=37)	13–18 (n=7)	*p*-value
Nausea and vomiting	23 (65.7%)	14 (58.3%)	0.565	14 (93.3%)	19 (51.4%)	4 (57.1%)	0.017
Neutropenia	31 (88.6%)	22 (91.7%)	0.699	13 (86.7%)	34 (91.9%)	6 (85.7%)	0.792
Thrombocytopenia	21 (60.0%)	15 (62.5%)	0.847	12 (80.0%)	22 (59.5%)	2 (28.6%)	0.067
Aanemia	20 (57.1%)	11 (45.8%)	0.393	13 (86.7%)	15 (40.5%)	3 (42.9%)	0.009
Diarrhoea	24 (68.6%)	12 (50.0%)	0.151	13 (86.7%)	18 (48.6%)	5 (71.4%)	0.033
Sepsis	9 (25.7%)	6 (25.0%)	0.951	7 (46.7%)	6 (16.2%)	2 (28.6%)	0.072
Mucositis	15 (42.9%)	11 (45.8%)	0.821	12 (80.0%)	12 (32.4%)	2 (28.6%)	0.005

Table-3: Association of age and gender with respect to tendencies towards red cell concentrates and GCSF administration (N=59)

Characteristics	Gender			Age (years)			
	Male (n=35)	Female (n=24)	*p*-value	<5 (n=15)	5-12 (n=37)	13-18 (n=7)	*p*-value
Red cell concentrates given	10 (28.6%)	19 (79.2%)	0.341	12 (80.0%)	14 (37.8%)	3 (42.9%)	0.021
Granulocyte-colony–stimulating factor given	13 (37.1%)	21 (87.5%)	0.656	8 (53.3%)	19 (51.4%)	7 (100%)	0.053

Table-4: Association of mortality with various chemotherapy induced toxicities (N=59)

Chemotherapy induced toxicities	Mortality		*p*-value
	Yes (n=11)	No (n=48)	
Nausea and vomiting	9 (81.8%)	28 (58.3%)	0.146
Neutropenia	11 (100%)	42 (87.5%)	0.216
Thrombocytopenia	8 (72.7%)	28 (58.3%)	0.377
Anemia	7 (63.6%)	24 (50.0%)	0.414
Diarrhoea	10 (90.9%)	26 (54.2%)	0.024
Sepsis	11 (100%)	4 (8.3%)	<0.001
Mucositis	6 (54.5%)	20 (41.7%)	0.438

DISCUSSION

This study highlights that younger age has a significant association with chemotherapy induced toxicity in children with Ewing sarcoma while the influence of gender is not statistically significant. The high incidence of chemotherapy-induced toxicities observed in this study is consistent with the broader international literature on Ewing sarcoma treatment in paediatric populations. Similar findings have been reported in studies conducted in other countries.[9,10] These toxicities not only impact the quality of life of paediatric patients but can also necessitate dose modifications or treatment delays, potentially affecting treatment outcomes.[11]

Ewing sarcoma is typically observed more frequently in children aged 10 years and older, and it traditionally exhibits a higher incidence in males, with a male-to-female ratio of 1.5.[12–14] This research also observed that 74.6% children with Ewing sarcoma were aged between 5–18 years with male predominance. There was no significant association between gender and chemotherapy-induced toxicities in our study. Contrary to our findings a study by Paioli *et al* in Italy found gender to significantly affect bone marrow toxicity with males having lower incidence of cytopenia and febrile neutropenia.[15] Safety data from another large muti-

centre EUROE.W.I.N.G.-99 study also reported females to have a higher incidence of adverse reactions regarding haemoglobin and platelets.[16] We found young age as a strong predictor for chemotherapy related toxicities with children under 5 years having worst outcome. Previous research has also shown young age as an independent risk factor for chemotherapy related adverse events.[15,16] This increased toxicity in young age could be attributed to variation in drug metabolism, pharmacokinetics and body fat distribution.

The study's findings regarding mortality due to neutropenic sepsis emphasizes the life-threatening nature of this complication in paediatric oncology.[17] This highlights the urgent need for robust infection control measures, early intervention, and vigilant monitoring, especially in patients at higher risk. Furthermore, the significant association between mortality and diarrhoea underscores the importance of gastrointestinal toxicity management at an earlier stage. The relationship between diarrhoea and mortality has been observed in other studies as well, emphasizing the need for effective prophylaxis and treatment of chemotherapy-induced diarrhoea.[18,19]

Conducting this study in Pakistan adds valuable regional context to the understanding of chemotherapy-induced toxicities in paediatric Ewing sarcoma in Low- and Middle-Income countries. It highlights the need for tailored supportive care strategies and resources to address the specific challenges faced by children with cancer in LMIC, including access to specialized medications and monitoring. Moreover, the study emphasizes the importance of developing comprehensive oncology care programs in LMIC which may face unique healthcare challenges. Collaboration between international and regional healthcare organizations and the adaptation of treatment protocols to local contexts could further improve outcomes for paediatric cancer patients in Pakistan. Being a single centre study conducted on a relatively small sample size without any longer follow up data were some of the limitations of this study.

CONCLUSION

Neutropenia, nausea and vomiting, thrombocytopenia, and diarrhoea were the most frequent chemotherapy induced toxicities in children with Ewing sarcoma. Relatively young age (below 5 years) was having strong association with chemotherapy induced adverse events including nausea and vomiting, anaemia, diarrhoea, and mucositis. Gender did not seem to influence related toxicities. Neutropenic sepsis and gastrointestinal adverse effects can be further investigated as predictors of mortality in these cases.

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