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Original Research Article

Impact of Delayed Chemotherapy Cycles on Remission Rates in Pediatric Sarcoma Patients

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Abstract: *Pediatric sarcomas, particularly Ewing sarcoma and osteosarcoma, are aggressive malignancies that require timely, protocol-based chemotherapy to maximize remission potential.* ***Objective:*** *To evaluate the effect of delayed chemotherapy cycles on remission rates in pediatric patients with Ewing sarcoma and osteosarcoma.* ***Methods:*** *This retrospective observational study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Center from 2023 to 2024. It included 150 pediatric patients (78 Ewing sarcoma, 72 osteosarcoma). A delayed cycle was defined as any cycle administered more than three days beyond the scheduled protocol date. Data on demographics, tumor type, delay causes, relative dose intensity (RDI), and remission status were collected from medical records.* ***Results:*** *Delays occurred in 92 patients (61.3%), most commonly due to hematologic toxicity (46.7%) and infections (30.4%). Overall remission rates were significantly higher in patients without delays (84.5%) compared to those with delays (58.7%, p = 0.001). In Ewing sarcoma, remission decreased from 79.4% in the no-delay group to 56.8% in the delayed group (p = 0.032), while in osteosarcoma, remission dropped from 91.7% to 60.4% (p = 0.004). Mean RDI was significantly lower in delayed patients (78.6% ± 8.9) versus on-time patients (93.4% ± 5.2, p < 0.001).* ***Conclusion:*** *Delayed chemotherapy cycles are associated with a significant reduction in remission rates in pediatric Ewing sarcoma and osteosarcoma, largely due to reduced dose intensity. Preventing delays through optimized supportive care and addressing logistical barriers should be prioritized to improve treatment outcomes.*

Keywords: Pediatric sarcoma, Ewing sarcoma, osteosarcoma, chemotherapy delay, remission rate, dose intensity

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Introduction

Pediatric sarcomas represent a relatively rare yet clinically significant category of childhood malignancies, accounting for approximately 10–15% of all pediatric cancers. The two most common subtypes are osteosarcoma and Ewing sarcoma, which usually occur when there is intensive growth in childhood or adolescence. They are highly aggressive, metastatic, and require intensive multimodal treatment (1). Modern sarcoma management is based on the combination of surgery, radiation therapy, and multi-agent chemotherapy, where chemotherapy has a pivotal role in the treatment of micrometastatic disease. It demonstrates improved long-term survival rates (2). These treatment regimens of chemotherapy are intentionally sequenced into specific sequences to maximize the killing of tumor cells by maintaining a continuous pressure of cytotoxicity agents that would enable the regeneration of normal cells (3). It is important to adhere to these schedules to maintain dose intensity of treatment, which studies have found to be directly proportional to the level of remissions and survival. Interruptions in the chemotherapy cycles may be due to the countless clinical, systemic, and patient-related causes (4). Clinically, hematologic side effects may result in a fall in the next cycle due to severe neutropenia or thrombocytopenia that may further cause complications, which are life-threatening. These interruptions can also be extended by infectious complications, especially in immunosuppressed pediatric patients (5).

The most critical concept in mitigating the impact of treatment delay is dose intensity, defined as the rate at which medicine is administered over time. Using both adult and pediatric clinical trials, numerous studies have shown that dose-intensity reduction, caused by missed doses, dose reductions, and delays, is an independent variable that results in worse outcomes, such as inferior remission rates and shorter event-free survival (6). In pediatric sarcomas, in which high-rate tumor growth and possible premature dissemination are established aspects, it is important to preserve planned dose density to avert disease progression and limit the development of chemoresistant cell clones (7). The effect of any delays, even a seemingly minimal one, can lead to the cumulative effect across the treatment plan and cause an observable dip in the cumulative dose intensity and consequently, in overall efficacy (8). Ewing sarcoma and osteosarcoma: the two most frequent malignant childhood and adolescent bone tumors provide important examples as to why it is essential to administer chemotherapy promptly in case of childhood malignancies (9). Even though they have been classified under the broad umbrella term of pediatric sarcomas, their biological underpinnings, treatment plans, and tolerance to treatment disruptions are quite dissimilar. Yet, in both cases, preservation of the chemotherapy schedule is closely related to the attainment of remission (10). During the times of rapid growth, osteosarcoma normally develops in the metaphyseal areas of long bones, most frequently around the knee. An early microscopic spread and tendencies towards pulmonary metastases characterise it. A neoadjuvant/surgery/adjuvant combination where high-dose multi-agent chemotherapy regimens (high-dose methotrexate, doxorubicin, and cisplatin or MAP protocol) have been used is a standard treatment modality (11). The preoperative (neoadjuvant) chemotherapy influences the shrinkage of the primary tumor, enhancement of the surgical resectability, and eliminates micrometastatic illness (12). This phase is one of the strongest indicators in the overall prognosis, as the percentage of tumor necrosis in a resected tumor is used as a histologic response (13). When there is a delay in the neoadjuvant cycles, the possibility of a low tumor necrosis rate may lead to incomplete resections or increased local recurrence. Likewise, disruption of adjuvant chemotherapy may prolong the post-surgery treatment period, allowing surviving micrometastatic cells even greater time to multiply and risk the probability of distant recurrence (14). Thus, this study is conducted to evaluate the effect of delayed chemotherapy cycles on remission rates in pediatric patients with Ewing sarcoma and osteosarcoma.

Methodology

This retrospective observational study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Center from 2023 to 2024. A total of 150 pediatric patients were included in the study. Of these, 78 were diagnosed with Ewing sarcoma and 72 with osteosarcoma, confirmed histopathologically. All patients aged ≤18 years at the time of diagnosis who had a confirmed histopathological diagnosis of Ewing sarcoma or osteosarcoma and who had received standard chemotherapy regimens according to institutional or cooperative group protocols were included. Only those who had completed at least the induction phase of chemotherapy and had documented follow-up imaging or histologic assessment to determine remission status were eligible. Patients with incomplete medical records, those lost to follow-up before completion of induction therapy, and those who had received part of their treatment at another institution without complete cycle timing documentation were excluded. Patient data were retrieved from hospital oncology files, chemotherapy administration logs, and the electronic medical record system. Information collected included demographic details such as age and gender, tumor type and site of the primary lesion, the chemotherapy regimen administered, and the intended cycle schedule. Dates of each chemotherapy cycle were reviewed to identify delays, and the cause of each delay, such as hematologic toxicity, non-hematologic toxicity, infections, or logistical issues, was documented. Remission status was recorded after the completion of the relevant treatment phase, and RDI was calculated for each patient using recorded dose and timing data.

All statistical analyses were performed using SPSS version 26. Descriptive statistics were applied to summarize demographic and clinical characteristics, with continuous variables expressed as mean ± standard deviation and categorical variables as frequencies and percentages. The chi-square test was used to compare remission rates between patients with and without delayed chemotherapy cycles. Statistical significance was set at a p-value less than 0.05.

Results

A total of 150 pediatric patients were included in the analysis, comprising 78 cases of Ewing sarcoma (52%) and 72 cases of osteosarcoma (48%). The overall mean age at diagnosis was 13.2 ± 3.1 years, with a slightly higher proportion of males (n = 86, 57.3%) compared to females (n = 64, 42.7%). The mean age for Ewing sarcoma patients was 12.8 ± 3.4 years, while for osteosarcoma patients it was 13.6 ± 2.8 years. There was a male predominance, with 86 males (57.3%) overall, including 44 males (56.4%) in Ewing sarcoma and 42 males (58.3%) in osteosarcoma. Female patients made up 64 cases (42.7%) overall. Delayed chemotherapy cycles occurred in 92 patients (61.3%), more frequently in osteosarcoma (48 patients; 66.7%) than in Ewing sarcoma (44 patients; 56.4%). On-time chemotherapy was completed in 58 patients (38.7%) overall, with a higher proportion in Ewing sarcoma (34 patients; 43.6%) compared to osteosarcoma (24 patients; 33.3%). (Table 1)

Table 1. Baseline Demographic and Clinical Characteristics of Patients (N = 150)

Characteristic	Total (N=150)	Ewing Sarcoma (n=78)	Osteosarcoma (n=72)
Mean Age (years) ± SD	13.2 ± 3.1	12.8 ± 3.4	13.6 ± 2.8
Male, n (%)	86 (57.3)	44 (56.4)	42 (58.3)
Female, n (%)	64 (42.7)	34 (43.6)	30 (41.7)
Delayed cycles, n (%)	92 (61.3)	44 (56.4)	48 (66.7)
On-time cycles, n (%)	58 (38.7)	34 (43.6)	24 (33.3)

Hematologic toxicity was the most common cause, affecting 43 patients (46.7%). Infectious complications were the second most frequent cause, observed in 28 patients (30.4%). Non-hematologic toxicity, such as mucositis or renal/hepatic impairment, accounted for delays in 12 patients (13.0%). Logistical or administrative issues, such as transportation problems or drug unavailability, were recorded in 9 patients (9.8%). (Table 2)

Table 2. Causes of Delayed Chemotherapy Cycles (n = 92)

Cause of Delay	n	% of Delayed Cases
Hematologic toxicity	43	46.7
Infectious complications	28	30.4
Non-hematologic toxicity	12	13.0
Logistical/administrative	9	9.8

In Ewing sarcoma, remission was achieved in 27 of 34 patients (79.4%) with no delay, compared to 25 of 44 patients (56.8%) with delays (p = 0.032). In osteosarcoma, 22 of 24 patients (91.7%) without delays achieved remission, compared to 29 of 48 patients (60.4%) with delays (p = 0.004). Overall, remission rates were significantly higher in the no-delay group (49 of 58 patients; 84.5%) compared to the delay group (54 of 92 patients; 58.7%), with a p-value of 0.001. (Table 3)

Table 3. Remission Rates by Delay Status and Tumor Type

Tumor Type	Delay Status	Remission Achieved n (%)	p-value
Ewing Sarcoma	No Delay (n=34)	27 (79.4)	0.032
	Delay (n=44)	25 (56.8)	
Osteosarcoma	No Delay (n=24)	22 (91.7)	0.004
	Delay (n=48)	29 (60.4)	
Overall	No Delay (n=58)	49 (84.5)	0.001
	Delay (n=92)	54 (58.7)	

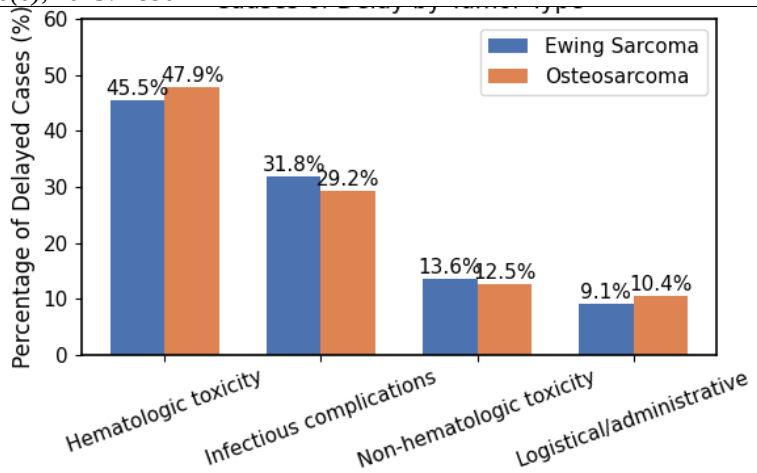

Figure 1: Causes of delay by tumor type

In Ewing sarcoma (n = 44 delayed cases), hematologic toxicity was the leading cause, affecting 20 patients (45.5%), followed by infectious complications in 14 patients (31.8%). Non-hematologic toxicities were seen in 6 patients (13.6%), and logistical or administrative reasons accounted for delays in 4 patients (9.1%). In osteosarcoma (n = 48 delayed cases), hematologic toxicity affected 23 patients (47.9%), infectious complications occurred in 14 patients (29.2%), non-hematologic toxicities in 6 patients (12.5%), and logistical or administrative reasons in 5 patients (10.4%). (Table 4)

Table 4. Causes of Delay by Tumor Type

Cause of Delay	Ewing Sarcoma (n=44)	Osteosarcoma (n=48)	Total (n=92)
Hematologic toxicity	20 (45.5)	23 (47.9)	43 (46.7)
Infectious complications	14 (31.8)	14 (29.2)	28 (30.4)
Non-hematologic toxicity	6 (13.6)	6 (12.5)	12 (13.0)
Logistical/administrative	4 (9.1)	5 (10.4)	9 (9.8)

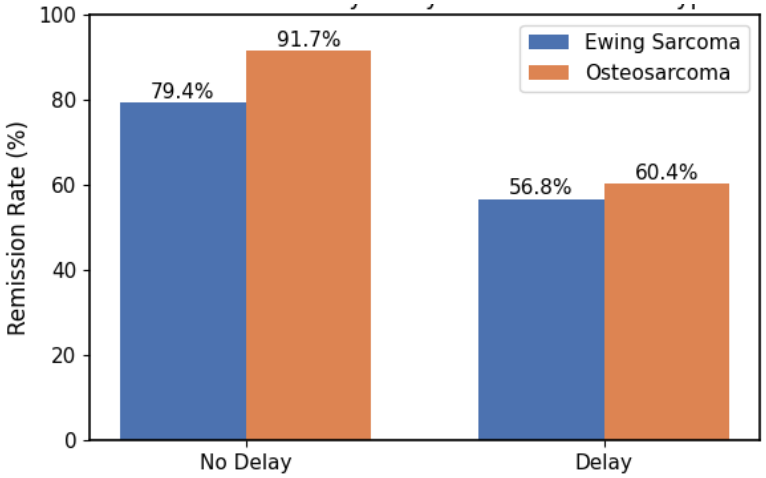

Figure 2: Remission rates by delay status and tumor type

Discussion

This study examined the impact of delayed chemotherapy cycles on remission rates in pediatric patients with Ewing sarcoma and osteosarcoma, involving a total of 150 patients treated at a tertiary care oncology center. The results prove the definite relation between chemotherapy delays and the decreased remission rates, and the impact is present in both tumor subtypes. The rate of remissions among patients who had no delay in their cycles was also lower. Still, it was significant overall (84.5% vs. 58.7%, p = 0.001), which underlines the need to maintain a strict adherence to the schedule of treatment of sarcoma in children. In Ewing sarcoma, the remission rate decreased 79.4 percent among patients with no delay of the cycle to 56.8 percent among patients with delayed cycles (p = 0.032). This is consistent with the current available evidence that Ewing sarcoma is known to be very chemosensitive but must be treated with tightly followed dose-compressed regimens to produce the best results (15). The results of our study support the idea that planned attraction of events may reduce survival, and the findings presented by previous cooperative group trials prove that decreasing the number of weeks in cycles to two weeks elevates event-free survival. Unplanned delays could undo such benefits (16). Due to the shorter doubling time and the possibility of early spreading of Ewing sarcoma, the treatment schedule interruptions might allow the tumor to re-grow and cause chemoresistance even with the smallest delay (17).

Overall, remission rates were lower in on-time patients (91.7%) compared to delayed patients (60.4%), with a significant difference (p = 0.004). The effective process of Osteosarcoma treatment is successfully based on the high rates of tumor necrosis during the neoadjuvant chemotherapy because the level of the histologic response is one of the primary prognostic factors. The delays in the neoadjuvant phase may lead to a decrease in the level of tumor necrosis, which will negatively affect surgical margins and raise recurrence probability (18). Our results are in line with other previous postulates that cumulative dose intensity and timely completion of adjuvant therapy are important prognostic factors concerning survival in osteosarcoma. The most frequent delay caused by hematologic conditions was 46.7 percent of the delayed cases, followed by infectious complications, 30.4 percent. The trend is not surprising, as both types of tumor are treated with multi-agent regimens characterized by myelosuppression (19). However, logistical or administrative reasons caused delays in almost 10% of cases, indicating possible, non-clinical obstacles to continuity of treatment that were preventable (20). Such results replicate the findings in low- and middle-income environments where the lack of infrastructure, drug supply, and transportation distances are key issues that lead to treatment disruption. The delayed group received significantly less (and clinically meaningful) relative dose intensity (RDI) of 78.6 percent (standard deviation of 8.9) than the on-time one (93.4 percent (standard deviation of 5.2). The significance of interdisciplinary cooperation is also strengthened in our results (21). The teams of pediatric oncology should be aligned with surgical and radiotherapy to avoid the occurrence where local control care is undermined because of delays in systemic therapy. Besides, in a limited resources environment, the collaboration between government health, non-governmental groups, and treatment facilities could be instrumental in improving both clinical and non-clinical factors contributing to delays. Although this study is well-supported by the harmful outcomes associated with delayed chemotherapy in pediatric sarcoma, it is prudent to note some limitations. The retrospective design has the potential of having selection bias, and confounding variables may have affected the result of remission. Besides, as a primary endpoint, the rate of remission was also considered, and further research is necessary to define the long-term outcome of treatment delay on event-free and overall survival.

Conclusion

It is concluded that delayed chemotherapy cycles significantly reduce remission rates in pediatric patients with Ewing sarcoma and osteosarcoma. In both tumor types, patients who completed treatment on schedule achieved markedly higher remission rates compared to those with unplanned delays, reflecting the critical importance of maintaining chemotherapy dose intensity and timing. Hematologic toxicity and infectious complications were the most frequent causes of delay, but nearly one in ten interruptions resulted from avoidable logistical or administrative issues.

Declarations

Data Availability statement
All data generated or analysed during the study are included in the manuscript.
Ethics approval and consent to participate
Approved by the department concerned. (IRBEC-MMS-24)
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Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

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All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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