

RESEARCH ARTICLE

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Predictors of Chemotherapy Induced Adverse Events in Pediatric Osteosarcoma Patients

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Abstract

Objective: To investigate the prevalence of chemotherapy-induced adverse events and the associated risk factors in pediatric patients with osteosarcoma. **Methods:** This retrospective cross-sectional study enrolled 90 pediatric osteosarcoma patients (with 1,017 chemotherapy cycles) treated at Srinagarind Medical Center, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand, between January 1, 2008 and December 31, 2018. The prevalence of major adverse events and a correlation between baseline characteristics and adverse events were analyzed using a generalized estimating equation model. **Result:** The prevalence of adverse events in 90 pediatric osteosarcoma patients (with 1,017 chemotherapy cycles) was determined as chemotherapy-induced nausea and vomiting (29.2%; n=296), hepatotoxicity (21.2%; n=215), anemia (70.69%; n=719), neutropenia (26.65%; n=271), and thrombocytopenia (13.65%; n=139). Factors associated with chemotherapy-induced hepatotoxicity included methotrexate dose ≥ 12 g/m² (odds ratio [OR] 1.30; 95% confidence interval [CI] 1.22–1.39; P<0.001), plasma concentration of methotrexate at 72 hours >0.1 μ M (OR 1.22; 95% CI 1.19–1.25; P<0.001), and pre-hydration rate ≤ 125 mL/m²/h (OR 1.10; 95% CI 1.07–1.12; P<0.001). **Conclusion:** Major adverse events are becoming more common in pediatric osteosarcoma patients, and risk factors include larger chemotherapy doses, higher plasma methotrexate concentrations, and a slower pre-hydration rate. The outcomes of the study could aid in the better treatment of toxicity in children with osteosarcoma.

Keywords: Osteosarcoma-adverse events- chemotherapy

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Introduction

Osteosarcoma is a common primary bone tumor of childhood and primarily located in the metaphysis of long bones (Jackson et al., 2016; Noah et al., 2016; Ksontini et al., 2018). It is ranked as the tenth most common pediatric malignancy in Thailand (Wiangon et al., 2011). The age-standardized incidence of osteosarcoma in individuals younger than 20 years is 3.1 per million per year (Wiangon et al., 2011), with a 5-year survival rate of 33.7% (Wiangon et al., 2011). Typically, 10% to 20% of patients have metastases at the time of diagnosis (Gianferante et al., 2017; Misaghi et al., 2018). A high burden of disease increases morbidity and mortality, compromising survival ability of affected patients (Misaghi et al., 2018). A multimodal treatment combining surgery and chemotherapy has been reported to increase a 5-year survival rate from 20% to 60% in patients with osteosarcoma (Jain and Kapoor, 2016).

Still, using combination treatment resulted in major adverse events (AE), such as gastrointestinal (GI) toxicities including chemotherapy-induced nausea and vomiting (CINV), mucositis, diarrhea, and hematologic toxicities, such as anemia, neutropenia, and thrombocytopenia (Janeway and Grier, 2010). A previous report evaluating a burden of adverse health outcomes demonstrated that 64% of pediatric osteosarcoma patients experienced a high or severe burden of AE particularly GI toxicity and nephrotoxicity (Geenen et al., 2007).

Considering factors associating with AE following osteosarcoma treatment, high-dose chemotherapy and intravenous (IV) hydration rate during high dose methotrexate (HD-MTX) were often described. Since the adverse events from pediatric osteosarcoma treatment are frequent, yet very few systematic AE reports among pediatric osteosarcoma patients are available. Therefore, we aimed to study the prevalence and risk factors associated with treatment-related AE in pediatric patients

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with osteosarcoma.

Materials and Methods

This retrospective cross-sectional study was conducted by reviewing the electronic medical records (EMRs) of 90 pediatric patients who received chemotherapy for osteosarcoma at the Department of Pediatrics, Srinagarind Medical Center, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand, between January 1st, 2008–December 31st, 2018. The study was approved by the Center for Ethics in Human Research, Khon Kaen University, Khon Kaen, Thailand (HE621309).

The inclusion criteria included patients aged less than 18 years with a histologically proven diagnosis of osteosarcoma, and receiving IV chemotherapy during hospitalization. Patients without records of MTX plasma concentration, AE outcome and AE management were excluded.

Chemotherapy regimen and IV hydration strategy

Pediatric patients with osteosarcoma were treated according to Thai Pediatric Oncology Group (TPOG) protocol (Thai Pediatric Oncology Group, 2016), which constitutes of neoadjuvant chemotherapy starting 10 to 14 weeks before surgery and adjuvant chemotherapy starting 1 to 3 weeks after surgery and continuing for 9 to 10 weeks. During the neoadjuvant phase, all patients received the MAP regimen (doxorubicin 37.5 mg/m²/day IV bolus for 2 days, cisplatin 60 mg/m²/day IV administered over 6 hours for 2 days every 2 weeks, HD-MTX 12 g/m²/day IV administered over 4 hours, and leucovorin 15 mg/m²/dose IV administered over 2 hours every 6 hours and started 24 hours after completing the MTX infusion to be given as a 2-weeks-on and 1-week-off therapy per treatment cycle). Subsequently, adjuvant chemotherapy was administered according to response criteria (Hanafy et al., 2018). For patients with good response (>90% tumor necrosis), the MAP regimen was continued. For those with a poor response demonstrating less than or equal to 90% tumor necrosis, the MAPI regimen would have been selected, with the addition of ifosfamide 2.4 g/m²/day IV administered over 1 hour once daily for 5 days, every 3 weeks, together with mesna 600 mg/m²/dose IV, given at 0, 3, 6, and 9 hours following ifosfamide administration.

In Addition, IV crystalloid fluid hydration was administered at a rate of 125 to 200 mL/m²/h at the physician's discretion. Sodium bicarbonate (40–60 mEq/L) was subsequently administered at least 12 hours before the MTX infusion to maintain a urinary pH of 7 or higher. Medications interfering with MTX clearance, such as nonsteroidal anti-inflammatory drugs (NSAIDs), cotrimoxazole, proton-pump inhibitors, and aspirin were suspended for up to 72 hours following MTX therapy.

Chemotherapy-induced AE

AEs (nausea, vomiting, mucositis, hepatotoxicity, nephrotoxicity, neurotoxicity, and bone marrow suppression) were retrospectively reviewed in all patients during and after each course of chemotherapy. AEs were confirmed by two pediatric oncologists based on clinical

manifestations and laboratory value available in the patient medication records and EMRs. All AE were assessed through Naranjo's algorithm, whereby a score greater than or equal to 5 means a probability of inclusion in the study (Naranjo et al., 1981). The severity of all AE was graded by using the Common Terminology Criteria for Adverse Events (CTCAE) version 5 (Constable et al., 2019). Rare AE (i.e., Fanconi's syndrome and encephalopathy) were confirmed by physicians based on computed tomography (CT) scanning and other relevant techniques.

Endpoints

The primary endpoint was the prevalence of chemotherapy-induced AE during the treatment of pediatric osteosarcoma. The secondary endpoint was the risk factor associated with chemotherapy-induced AE.

Statistical analysis

The baseline characteristics were analyzed using descriptive statistics. The prevalence of AE was reported in terms of frequency and percentage. The correlation between risk factors and AE was analyzed using the generalized estimating equation (GEE) model. A sample size of 86 patients was required to achieve 80% power to detect a 10% prevalence of AE (Traivaree et al., 2018). Statistical significance was based on the two-sided test with P<0.05. STATA version 16 (StataCorp LP, College Station, TX, USA) was used for statistical analyses and data management.

Results

Ninety pediatric patients with osteosarcoma who were treated during the study period were included and 1,017 chemotherapy cycles were reviewed. The majority of patients were female (52.22%), and the median age at diagnosis was 11.18±2.69 years; and 53% had metastatic disease at diagnosis and lung was the most extensive site of distant metastasis (43.33%). The most common subtype of osteosarcoma was the osteoblastic type (73.33%), and the distal femur was the most frequent tumor location (43.33%). All baseline demographic data are shown in Table 1.

AEs reports included GI toxicities, hematologic toxicities, nephrotoxicity, and neurotoxicity. The most frequent adverse event was anemia (70.69%). The other hematologic toxicities included neutropenia, febrile neutropenia, and thrombocytopenia (prevalence of 20.69%, 1.73%, and 13.65%, respectively). Grade 2 severity anemia and neutropenia were observed in 34.32% and 10.13% of the patients, respectively. The severity of thrombocytopenia was only seen in Grade 1 (7.76%). The prevalence of CINV was 29.2%, of which the majority were grade 3 to 4 severity (15.90%). The prevalence of hepatotoxicity was 21.2%, of which the majority was grade 3 in severity (8.67%). The most common nephrotoxicity included acute kidney injury (1.37%) and electrolyte imbalance (1.67%). The prevalence and severity grading of all other AE are shown in Table 2.

Even though it is rarely reported, a Fanconi's syndrome was identified in a 12-year-old girl with osteosarcoma

Table 1. Baseline Characteristics

Characteristics	No. (n=90) (%)
Sex	
Male	43 (47.78)
Female	47 (52.22)
Age at diagnosis median+/- IQR	11.18±2.69
Age group, years	
0-5	2 (2.22)
6-10	26 (28.89)
11-15	62 (68.89)
BMI (age percentile)	
Underweight	23 (25.56)
Normal	49 (54.44)
Overweight	8 (8.89)
Obesity	10 (11.11)
Osteosarcoma	
Conventional type*	84 (93.33)
Telangiectatic type	4 (4.44)
Chondromyxoid fibroma	1 (1.11)
Small cell osteosarcoma	1 (1.11)
Tumor site	
Distal femur	40 (44.44)
Proximal tibia	22 (24.44)
Proximal humerus	10 (11.11)
Distal tibia	7 (7.78)
Proximal femur	5 (5.56)
Maxilla	4 (4.44)
Fibula	1 (1.11)
Sphenoid bone	1 (1.11)

BMI, body mass index; *Conventional type consists of osteoblastic, chondroblastic, and fibroblastic subtypes

Table 2. Prevalence and Severity of Adverse Events

Events (N=1,017)	No. (%)	95% CI
Chemotherapy-induced nausea and vomiting	296 (29.10)	0.26-0.32
Grade 1-2	134 (13.20)	0.11-0.15
Grade 3-4	162 (15.90)	0.13-0.18
Mucositis	69 (6.79)	0.05-0.08
Grade 1-2	31 (3.05)	0.02-0.04
Grade 3-4	38 (3.74)	0.02-0.05
Hepatotoxicity	215 (21.19)	0.18-0.24
Grade 1-2	104 (10.25)	0.08-0.12
Grade 3-4	111 (10.94)	0.09-0.13
Anemia	719 (70.79)	0.67-0.73
Grade 1-2	602 (59.19)	0.56-0.62
Grade 3-4	118 (11.60)	0.09-0.14
Neutropenia	271 (26.55)	0.24-0.29
Grade 1-2	109 (10.72)	0.08-0.13
Grade 3-4	161 (15.83)	0.14-0.18
Thrombocytopenia	139 (13.65)	0.12-0.16
Grade 1-2	93 (9.13)	0.07-0.11
Grade 3-4	46 (4.52)	0.03-0.05

CI, confidence interval

undergoing ifosfamide 2.4 g/m² IV for five consecutive days. The laboratory results revealed abnormal blood

Events (N=1,017)	Total AE	Gr 1-2	Gr 3-4
CINV	29.1	13.2	15.9
Mucositis	6.79	3.05	3.74
Hepatotoxicity	21.19	10.25	10.94
Anemia	70.79	59.19	11.6
Neutropenia	26.55	10.72	15.83
Thrombocytopenia	13.65	9.13	4.52

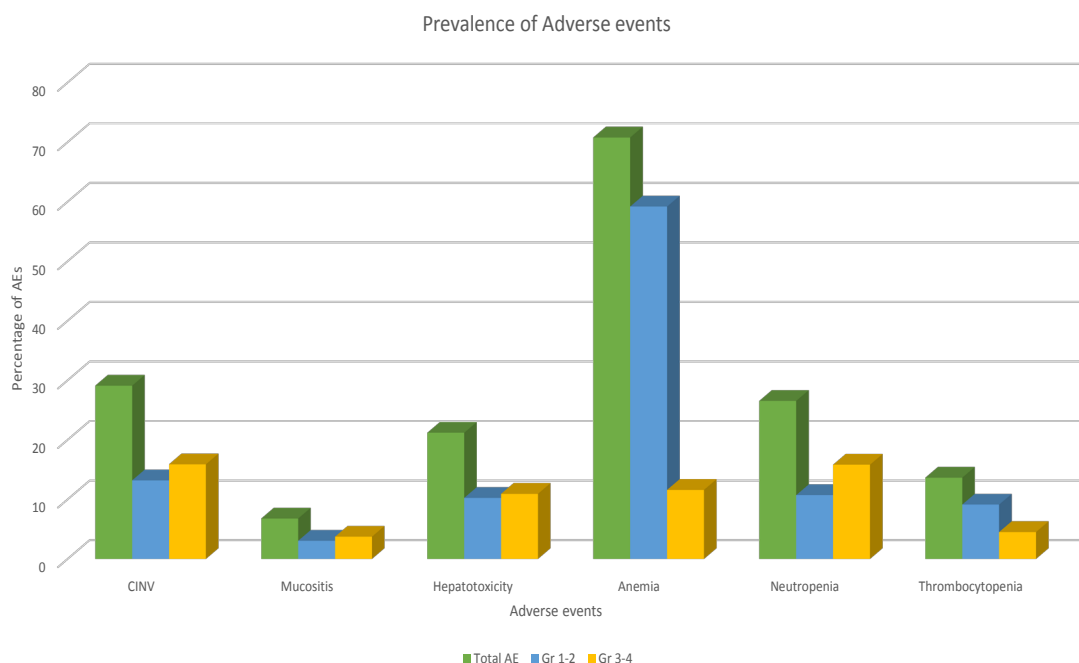


Figure 1. Prevalence of Adverse events. AE, Adverse event; CINV, Chemotherapy induced nausea and vomiting; GR, Grade

Table 3. Results of Univariable Analysis for Risk Factors Associated with Adverse Events

Factors	Hepatotoxicity		Anemia		Neutropenia		Thrombocytopenia	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age								
≤ 10 years	1	reference	1	reference	1	reference	1	reference
> 10 years	1.01	0.94–1.09	0.99	0.89–1.09	1.01	0.96–1.04	0.99	0.89–1.09
Sex								
Male	1	reference	1	reference	1	reference	1	reference
Female	0.92	0.85–0.98	1.04	0.95–1.14	0.99	0.95–1.03	0.99	0.96–1.03
Body mass index								
Normal	1	reference	1	reference	1	reference	1	reference
Underweight	0.97	0.88–1.07	0.98	0.88–1.09	1.01	0.98–1.10	0.98	0.88–1.09
Cumulative dose of cisplatin								
<300 mg/m ²	1	reference	1	reference	1	reference	1	reference
≥300 mg/m ²	1.32	1.19–1.44	1.07	0.97–1.17	0.97	0.95–1.00	1.04	0.99–1.02
Cumulative dose of ifosfamide								
<60 g/m ²	1	reference	1	reference	1	reference	1	reference
≥60 g/m ²	0.87	0.75–0.99	1.03	0.93–1.14	1.04	0.97–1.06	0.97	0.91–1.03
Dose of methotrexate								
<12 g/m ²	1	reference	1	reference	1	reference	1	reference
≥12 g/m ²	1.58	1.56–1.60	1.15	1.02–1.29	0.98	0.94–1.03	1.07	1.03–1.11
Methotrexate level at 72 hours								
≤0.1 µg/L	1	reference	1	reference	1	reference	1	reference
>0.1 µg/L	1.58	1.51–1.68	0.95	0.93–0.99	0.9	0.88–0.93	0.97	0.94–0.98
Pre-hydration rate								
>125 mL/m ² /h	1	reference	1	reference	1	reference	1	reference
≤125 mL/m ² /h	1.15	1.13–1.15	1.04	1.01–1.08	1.14	1.09–1.18	1.1	1.02–1.05

CI, confidence interval; OR, odds ratio

chemistries as follows: hypokalemia (K 2.9 mEq/L), hypomagnesemia (Mg 1 mEq/L), hypophosphatemia (phosphate- 3 mEq/L), and metabolic acidosis (bicarbonate 18 mEq/L). Urinalysis showed proteinuria and glucosuria which was consistent with Fanconi's syndrome. The probability of ifosfamide-induced Fanconi's syndrome in this patient was assessed by the Naranjo Adverse Drug Reaction Probability Scale and classified as probable (Naranjo et al., 1981).

A rare neurological AE, encephalopathy, were also reported in three patients. The first patient, a 14-year-old girl diagnosed with osteosarcoma with lung metastasis receiving IV MTX 12 g/m² at week 13 of the treatment course. Seven days after MTX was administered, the patient experienced alteration of consciousness with drowsiness, speechlessness, and seizures. Laboratory results showed normal serum electrolytes (Na 138 mEq/L, K 4.4 mEq/L, Ca 8.3 mEq/L, Mg 1.5 mEq/L, and phosphate- 4.4 mEq/L) and normal renal function. A brain CT showed no evidence of gross brain parenchymal lesion, intracranial hemorrhage, or venous sinus thrombosis. Subsequently, the patient's serum MTX concentration was taken and got supratherapeutic (2.3 µM). The patient was symptomatically treated at the physician's discretion with 10 mg diazepam, and 5 mg of folic acid administered orally. Her clinical condition

improved within 2 days after symptomatic treatment. The MTX-induced encephalopathy probability was assessed by the Naranjo Adverse Drug Reaction Probability Scale and classified as probable (Naranjo et al., 1981). Hence, her encephalopathy was probably related to supra-therapeutic MTX serum concentration.

The second patient, a 12-year-old female diagnosed with metastatic osteosarcoma being treated with IV MTX 9.6 g/m² at week 24 of the treatment course. Two days following MTX administration, the patient developed seizures and alteration of consciousness. Blood biochemistry results were within normal limit including Na 134 mEq/L, K 3.9 mEq/L, Cl 93 mEq/L, Ca 10 mEq/L, Mg 2 mEq/L, phosphate- 4.3 mEq/L, blood urea nitrogen (BUN) 8.3 mg/dL, and serum creatinine (sCr) 0.3 mg/dL. A brain CT scan revealed no evidence of brain gross focal lesions or abnormal leptomeningeal enhancement. Her serum MTX concentration level obtained was 0.19 µM at 48 hours and 0.04 µM at 58 hours which was consistent with delayed MTX clearance (Inaba et al., 2008). This patient was symptomatically treated with one dose of 2 mg intramuscular vitamin B complex and 5 mg folic acid administered orally. She recovered after 2 days of supportive treatment. The MTX-induced encephalopathy probability was assessed by the Naranjo Adverse Drug Reaction Probability Scale and classified as probable

Table 4. Results of Multivariable Analysis for Risk Factors Associated with Adverse Events

Factors	Hepatotoxicity		Anemia		Neutropenia		Thrombocytopenia	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Cumulative dose of cisplatin								
<300 mg/m ²	1	reference	1	reference	1	reference	1	reference
≥300 mg/m ²	0.97	0.9–1.04	1.02	0.78–1.31	0.98	0.85–1.15	1.36	1.29–1.33
Cumulative dose of ifosfamide								
<60 g/m ²	1	reference	1	reference	1	reference	1	reference
≥60 g/m ²	0.98	0.8–1.09	1.12	0.89–1.40	0.96	0.84–1.09	1.37	1.28–1.45
Dose of methotrexate								
<12 g/m ²	1	reference	1	reference	1	reference	1	reference
≥12 g/m ²	1.3	1.22–1.39	1.14	0.89–1.46	1.9	1.34–2.70	1.11	1.03–1.18
Methotrexate level at 72 hours								
≤0.1 µg/L	1	reference	1	reference	1	reference	1	reference
>0.1 µg/L	1.22	1.19–1.25	1.75	1.12–2.75	3.32	1.47–7.49	2.15	1.72–2.69
Pre-hydration rate								
>125 mL/m ² /h	1	reference	1	reference	1	reference	1	reference
≤125 mL/m ² /h	1.1	1.07–1.12	1.03	1.01–1.05	1.12	1.07–1.17	1.07	1.04–1.10

CI, confidence interval; OR, odds ratio

(Naranjo et al., 1981). Therefore, encephalopathy in this patient was also probably related to MTX therapy.

The third patient, a 13-year-old girl diagnosed with osteosarcoma of the proximal humerus being treated with intravenous ifosfamide 2.65 g/m² for three consecutive days. Following the first treatment day, the patient developed alteration of consciousness, drowsiness and seizures. The laboratory results were normal (Na 139 mEq/L, K 3.5 mEq/L, Cl 104 mEq/L, Ca 10.1 mEq/L, Mg 2.1 mEq/L, phosphate- 4.4 mEq/L, BUN 7.1 mg/dL, and sCr 0.5 mg/dL). A brain CT revealed no gross focal lesion evidence or abnormal leptomeningeal enhancement in the brain. A loading dose of 800 mg IV phenytoin was administered to control her seizure. Her symptoms were improved 2 days after discontinuing ifosfamide. The probability of ifosfamide-induced encephalopathy in this patient was probable per the Naranjo Adverse Drug Reaction Probability Scale (Naranjo et al., 1981). Thus, encephalopathy in this patient was probably related to ifosfamide treatment.

Subsequently, an univariable and multiple variable analysis to investigate association between risk factors and AE were performed as shown in Tables 3 and 4. The results revealed that MTX doses greater than or equal to 12 g/m², delayed MTX clearance greater than or equal to 72 hours, and pre-hydration rates of less than or equal to 125 mL/m²/h significantly increased risks of hepatotoxicity and hematologic toxicities. In addition, a cumulative dose of cisplatin greater than or equal to 300 mg/m² (OR 1.36; 95% CI 1.29–1.33; P=0.023) and a cumulative dose of ifosfamide greater than or equal to 60 g/m² (OR 1.37; 95% CI 1.28–1.45; P=0.033) significantly increased the risk of thrombocytopenia

Discussion

In pediatric osteosarcoma, the standard chemotherapy

regimen consists of cisplatin, doxorubicin, MTX, and ifosfamide administered as combination therapy (Jain and Kapoor, 2016). In this study, the prevalence of GI toxicities, including CINV, was 29.2%, whereas the prevalence of hepatotoxicity and mucositis was 21.2% and 6.80%, respectively. These prevalence rates of AE are consistent with previous reports (Traivaree et al., 2018; Xu et al., 2014), particularly CINV, hepatotoxicity, and mucositis that were observed in 28%, 23%, and 8.7% of patients, respectively. Interestingly, the prevalence of anemia in this study was much higher than that of early report by Marina et al. (Marina et al., 2016) (70.69% vs 10%). The disagreement observed could have been due to a misclassification bias, as thalassemia patients were not excluded from this study. In addition, the prevalence of neutropenia, febrile neutropenia, and thrombocytopenia prevalence (26.65%, 1.73%, and 13.65%, respectively) were much lower than that of Marina et al (94%, 50%, and 93% respectively). Since the use of granulocyte colony-stimulating factor as primary prophylaxis was recommended in pediatric osteosarcoma according to the TPOG protocol, this might have explained the lower incidence of hematologic toxicity in the study setting.

For the association analysis, GEE was chosen to analyze response correlation. GEE is an extension of the generalized linear model for statistical hypothesis testing, which determines the influence of factors on repeated measures of dependent variables comprising binary outcomes that are collected from subjects over time (Hu et al., 1998; Oduyungbo et al., 2008; Stillman, 2003; Ballinger, 2004). To confront with intra-cluster correlation, the covariance matrix is adjusted for estimating parameters by GEE. GEE robustness is another advantage that generated good estimates of the regression parameters (Zorn, 2001).

In the univariable analysis, there was no correlation between age, sex, body mass index, and AEs. In the

multivariable analysis, risk factors associated with hepatotoxicity and hematologic toxicities included MTX doses greater than or equal to 12 g/m², pre-hydration rates less than or equal to 125 mL/m²/h, and delayed MTX clearance (≥ 72 hours). These results agree with the observations from Özdemir et al (2016) and Lin et al (2009) wherein MTX doses greater than 3 g/m² and delayed MTX clearance (≥ 48 hours) increased risks of both hepatotoxicity and hematologic toxicities. Furthermore, aggressive pre-hydration rates able to reduce the frequency of AE was also reported by Relling et al (1994) and Karremann et al (2014). Hence, the study findings implied that patients undergoing osteosarcoma treatment should be treated with crystalloid fluid hydration at pre-hydration rates of more than 125 mL/m²/h. Apart from factors described above, higher cumulative doses of cisplatin and ifosfamide appeared to associate with thrombocytopenia. These results were consistent with the two studies conducted by Fan et al (2015) and Tamamyan et al (2016) reporting an increased thrombocytopenia risk (relative risk [RR] 1.92, 95% CI 1.23–3.01; P=0.004) with ifosfamide-based regimens, previous treatment exposure to cisplatin and MTX.

The standard chemotherapy in osteosarcoma could have also induced nephrotoxicity predominantly in patients who received cumulative cisplatin doses greater than or equal to 300 mg/m² and cumulative ifosfamide doses greater than or equal to 60 g/m² (Perazella, 2012). The prevalence of acute kidney injury and electrolyte imbalance (hypomagnesemia and hypokalemia) in this study were 1.37% and 1.67%, respectively, as similarly observed in previous report (Oberlin et al., 2009). Rarely, Fanconi's syndrome could have been observed in patients receiving cumulative ifosfamide doses greater than or equal to 90 g/m² (Ho et al., 1995; Skinner et al., 2000). Likewise, Langer et al (2004) reported a 1% prevalence of Fanconi's syndrome in patients who were treated with higher cumulative doses of cisplatin and ifosfamide (Aleksa et al., 2001; Ruggiero et al. 2017) Concordance with the study Fanconi's syndrome was observed and risk factors associated with Fanconi's syndrome in the study might have been related to history of previous treatments with cumulative cisplatin doses greater than or equal to 360 mg/m² and HD-MTX (Hall et al., 2014; Oberlin et al., 2009).

According to the three cases above, encephalopathy was observed. A hypothetically related to MTX-induced encephalopathy (Inaba et al., 2008; Vezmar et al., 2003; Rubnitz et al., 1998) possibly relates to a substantially increased homocysteine level, leading to oxidative stress and neuronal death. In contrast, ifosfamide could have induced encephalopathy through its toxic metabolite chloroacetaldehyde (Ajithkumar et al., 2007). Symptoms normally occur within 2–96 hours after ifosfamide administration. From the encephalopathy case series described in this study, the plausible risk factors being MTX dose ≥ 12 g/m² and delayed MTX clearance were in accordance with previous reports as encephalopathy was observed among patients aged greater than 10 years, receiving higher doses of MTX (≥ 8 g/m²), and possessed a delayed MTX clearance (≥ 42 hours) (Bhojwani et al.,

2014; Dufourg et al., 2007; Inaba et al., 2008; Rubnitz et al., 1998).

In terms of ifosfamide-induced encephalopathy, the possible risk factors according to the case described in this study might have been related to prior nephrotoxic agents exposure such as history of platinum-based treatment which was consistent with several observations (David and Picus, 2005; Tajino et al., 2010).

This is foremost the largest study to identify the prevalence of chemotherapy-induced AE in pediatric patients with osteosarcoma in Thailand. This research was conducted at a large-scale tertiary care medical center, thereby contributing to a larger sample size than previously reported studies. Our results might have some clinical implications in optimizing pediatric osteosarcoma toxicity management. The pre-hydration rates >125 mL/m²/h should be maintained in patients undergoing systemic treatment of osteosarcoma to prevent major AE. Therapeutic drug monitoring should be performed in with high HD-MTX and delayed MTX clearance.

There are some limitations as a cross-sectional design is not ideal to describe a causal relationship between drugs and AEs, and might have led to an underestimation of the prevalence of rare AEs (Levin, 2006; Kesmodel, 2018; Flanelly and Jankowski, 2014). Nevertheless, the study results confirmed magnitudes and distributions of association between risk factors, including MTX doses ≥ 12 g/m², delayed MTX clearance (≥ 72 hours), and pre-hydration rates of less than or equal to 125 mL/m²/h as previously reported in a cohort study (Puts et al., 2014).

The administration of chemotherapy in pediatric patients with osteosarcoma led to the major AE, including GI and hematologic toxicities. The prevalence of adverse outcomes was higher in the studied risk group. The results of this study have potential implications for the prevention and monitoring of AE in pediatric patients with osteosarcoma who receive chemotherapy in Thailand.

Author Contribution Statement

Conceptualization, P.S., P.K. and S.S.; methodology, P.S., P.K. and S.S.; formal analysis, P.S. and S.S.; data curation, P.S., J.Y. and S.S.; writing—original draft preparation, P.S., P.K., J.Y., M.S., S.C. and S.S.; writing—review and editing, P.S., P.K., J.Y., M.S., S.C. and S.S. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest

Institutional Review Board Statement

The study was conducted according to guidelines of the Declaration of Helsinki and approved by the Center for Ethics in Human Research, Khon Kaen University, Khon Kaen, Thailand (HE621309).

Informed Consent Statement

Patient consent was waived due to the retrospective study design by the Center for Ethics in Human Research, Khon Kaen University, Khon Kaen, Thailand.

Availability of data

No additional data were generated in the study.

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