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INTEGRATIVE REVIEW ARTICLE

MANAGEMENT OF ADVERSE EFFECTS OF ANTINEOPLASTIC AGENTS IN CHILDREN AND ADOLESCENTS WITH OSTEOSARCOMA: AN INTEGRATIVE REVIEW

MANEJO DOS EFEITOS ADVERSOS DOS ANTINEOPLÁSICOS EM CRIANÇAS E ADOLESCENTES COM OSTEOSARCOMA: REVISÃO INTEGRATIVA

MANEJO DE LOS EFECTOS ADVERSOS DE AGENTES ANTINEOPLÁSICOS EN NIÑOS Y ADOLESCENTES CON OSTEOSARCOMA: REVISIÓN INTEGRADORA

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ABSTRACT

Objective: identifying interventions for adverse effects of antineoplastic agents in children and adolescents with osteosarcoma. ***Method:*** an integrative review, with a view to answering the guiding question << What are the interventions for the management of adverse effects of antineoplastic agents in children and adolescents with osteosarcoma? >> The query was on PubMed/ MEDLINE, LILACS, CINAHL, and Cochrane IBECS virtual library data. The descriptors were: chemotherapy, child, and adolescent osteosarcoma. ***Results:*** the sample consisted of eight researchers. Pharmacological interventions for prevention and control of toxicities were centered on various bodily functions. ***Conclusion:*** the evidence presented recommendations with a strong level of evidence for the control of adverse effects of chemotherapy in children and adolescents diagnosed with osteosarcoma and are restricted to drug therapy. ***Descriptors:*** Chemotherapy, Child, Adolescent, Osteosarcoma.

RESUMO

***Objetivo*:** identificar intervenções para efeitos adversos dos antineoplásicos em crianças e adolescentes com osteosarcoma. ***Método*:** revisão integrativa, com vistas a responder a pergunta norteadora << Quais são as intervenções para manejo de efeitos adversos dos antineoplásicos em crianças e adolescentes com osteosarcoma? >> A consulta foi nas bases de dados PubMed/MEDLINE, LILACS, CINAHL, IBECS e biblioteca virtual Cochrane. Os descritores foram: quimioterapia, criança, adolescente e osteosarcoma. ***Resultados*:** oito compuseram a amostra da pesquisa. As intervenções farmacológicas para prevenção e controle de toxicidades foram centradas nas diversas funções orgânicas. ***Conclusão*:** as evidências apresentam recomendações com forte nível de evidência para o controle de efeitos adversos no tratamento quimioterápico de crianças e adolescentes com diagnóstico de osteosarcoma e estão restritas à terapêutica medicamentosa. ***Descritores*:** Quimioterapia, Criança, Adolescente, Osteosarcoma.

RESUMEN

Objetivo: identificar las intervenciones para los efectos adversos de los agentes antineoplásicos en los niños y adolescentes con osteosarcoma. ***Método:*** una revisión integradora con el fin de responder a la pregunta guía << ¿Cuáles son las intervenciones para el manejo de los efectos adversos de los agentes antineoplásicos en los niños y adolescentes con osteosarcoma? >> La consulta ocurrió en PubMed/MEDLINE, LILACS, CINAHL y Cochrane IBECS datos de la biblioteca virtual. Los descriptores fueron: la quimioterapia, niño, adolescente y osteosarcoma. ***Resultados:*** La muestra estuvo constituida por ocho investigadores. Intervenciones farmacológicas para la prevención y control de las toxicidades se centraron en varias funciones corporales. ***Conclusión:*** la evidencia presentada recomendaciones con un fuerte nivel de evidencia para el control de los efectos adversos de la quimioterapia en los niños y adolescentes con diagnóstico de osteosarcoma y se limitan a la terapia con medicamentos. ***Descriptores:*** Quimioterapia, niño, adolescente, osteosarcoma.

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INTRODUCTION

Cancer is a public health problem, considering its high percentage of incidence, morbidity, mortality and social impact. In Latin America, cancer is the third leading cause of death. In Brazil, cancer is responsible for about 15,5% of the deaths, which represents the second cause of mortality, behind cardiovascular disease. It is vital for early diagnosis of malignant neoplasms, in which local control and the therapeutic approach aimed at increasing the survival rate of patients are needed. The National Cancer Institute (NCI) estimated the incidence of 518.510 new cases of cancer in Brazil in 2012, and this estimate is also valid for the year 2013.[1-2]

Among the cancers in general, primary bone tumors constitute 3% to 4%. The diagnosis of malignant bone tumors is even later in our country. The osteosarcoma (OS) is the most prevalent malignancy of human bone structure. This bone tumor, with most frequent primary malignant bone matrix, representing 0,2% of human malignancies. First described in 1805 by Dupuytren has as main feature the production of osteoid matrix by neoplastic cells.[2]

Annually in the United States, the incidence of OS it reaches 900 new cases, or 6,5 cases per million children. It is estimated that the incidence in Brazil reaches about 350 cases/year up to 20 years.[3-4]

The OS has unknown and affects mainly children and adolescents in the first two decades of life, especially at the stage where there is bone growth etiology. The OS is also seen most commonly in people over 60 years of age. The initial involvement in 75% of cases occurs in the metaphysis of long bones, with subsequent progression to epiphysis[1]. The most frequently affected sites are the distal femur and proximal tibia, followed by the proximal humerus and pelvis, and shaft[5]. In the presence of metastasis is the commonest site is the lung. The onset of symptoms may be manifested by a history of trauma to the affected limb with reports of localized pain that lasts for several months.[6]

Above the 70 patients with OS were treated exclusively with surgery, which resulted in limb amputation. The prognosis for systemic relapse usually occurs within six months and resulted in death in 90% of cases.[7]

The prognosis of patients with osteosarcoma depends on the size of the tumor, the free margins and the presence of lung metastases. It is understood that a person's prognosis varies depending on osteosarcoma discovery time, her age, size, location of the primary tumor, metastasis and especially the response of the patient towards the neoadjuvant chemotherapy.[6-7]

Current treatment protocols for the OS are based on the association of cancer chemotherapy adjuvant and neoadjuvant radiotherapy and cirurgia8. Presently, several clinical studies emphasize the effectiveness of the result when the surgical treatment is associated with chemotherapy, which contributes to the reduction of the tumor size and increasing the possibility of cure.[6-7]

The antineoplastic multidrug therapy is a treatment modality that enables higher survival rate. The combination of drugs that have action in different cell cycle phases provide increased effectiveness in fighting cancer cells. The drugs used in protocols for treatment and palliation include primarily classes, namely: antimetabolites (metotrexatoto and etoposide), alkylating (cisplatin, carboplatin, cyclophosphamide and ifofosfamida) and antitumor antibiotics (doxorubicin, bleomycin and dactinomycin).[9]

It is understood that cancer chemotherapy may have efficacy in the treatment for, but there are cases that the patient can undergo limb amputation, considering the degree of involvement and tumor location. In some cases it is possible to perform the removal of the tumor, allowing the preservation of the member.[8]

Chemotherapy treatment is considered effective. However, at the same time presents as an aggressive therapy to the body due to its high specificity for its toxicity cell activity that triggers structural, biochemical and physiological changes.[10]

Among the consequential adverse effects of antineoplastic toxicity of chemotherapy in the treatment of osteosarcoma, the prevalent hematologic changes with a picture of leukopenia, thrombocytopenia and anemia. Other changes may appear as gastrointestinal toxicities symptoms of nausea and vomiting, mucositis and signs, which may signal an inflammatory response and mucosal membranes. Associated with this change are symptoms of diarrhea or constipation depending on which drug is being administered to the patient. The antineoplastic chemotherapy can trigger cardiac toxicities, hepatic, pulmonary, neurological, bladder, renal, metabolic, dermatological, allergic reactions and fatigue.[9]

Concerning the clinical practice, interventions to decrease the adverse effects related to chemotherapy should be studied to minimize interference in the treatment of cancer patients and enable comfort to these patients. The evidence-based practice is being widely discussed and disseminated in areas related to health care knowledge. Thus one can recognize that the methodological rigor and selection of evidence related to the adverse effects of antineoplastic treatment for OS will provide the best care practices and behaviors to patients[11-12]. Given the above, this study aimed to identify interventions to control the signs and symptoms of adverse events in children and adolescents with osteosarcoma treated with antineoplastic therapy effects.

METHOD

It is an integrative literature review. This is a methodology that provides recovery from existing data for selection and construction of evidence-based practice.[13]

We used the PICO strategy (acronym for patient, intervention, comparison and outcome)[14] to construct the guiding question: What are the interventions for the management of adverse effects of antineoplastic chemotherapy in children and adolescents with osteosarcoma?

The databases used were the Cochrane Library, PubMed/MEDLINE (System Analysis and Retrieval of Medical Literature Online) (Latin American and Caribbean Literature on Health Sciences) LILACS, CINAHL (Cumulative Index of Nursing and Literature Data of Health), IBECS (Spanish Bibliographic Index of Health Sciences). Controlled descriptors used to search in Portuguese and English were (MeSH/MeSH): chemotherapy ("therapy drug") and/and child (child) and/and teenager (adolescent) and/and osteosarcoma (osteosarcoma). Studies who participated in the selection were published in English, Spanish and Portuguese.

Scientific articles that addressed interventions to children and adolescents (0-18 years) diagnosed with osteosarcoma undergoing chemotherapy in order to control adverse effects of these drugs were included. The purpose of this study was to identify the pharmacological and non-pharmacological interventions for adverse effects in subjects who were treated with chemotherapy alone or in combination with radiotherapy and surgery, since the results of the studies were treated in isolation.

Reading and interpretation of studies was adapted an instrument to obtain data.[15] The articles were classified according to their level of evidence and grade of recommendation. For this we used the Classification table prepared by the Centre for Evidence Based Medicine, University of Oxford.[16]

RESULTS

1687 articles were found. After thorough reading, studies that were in duplicate and those who did not contemplate the inclusion criteria were excluded. 8 articles published in the period 1993-2013, all being in English were analyzed.

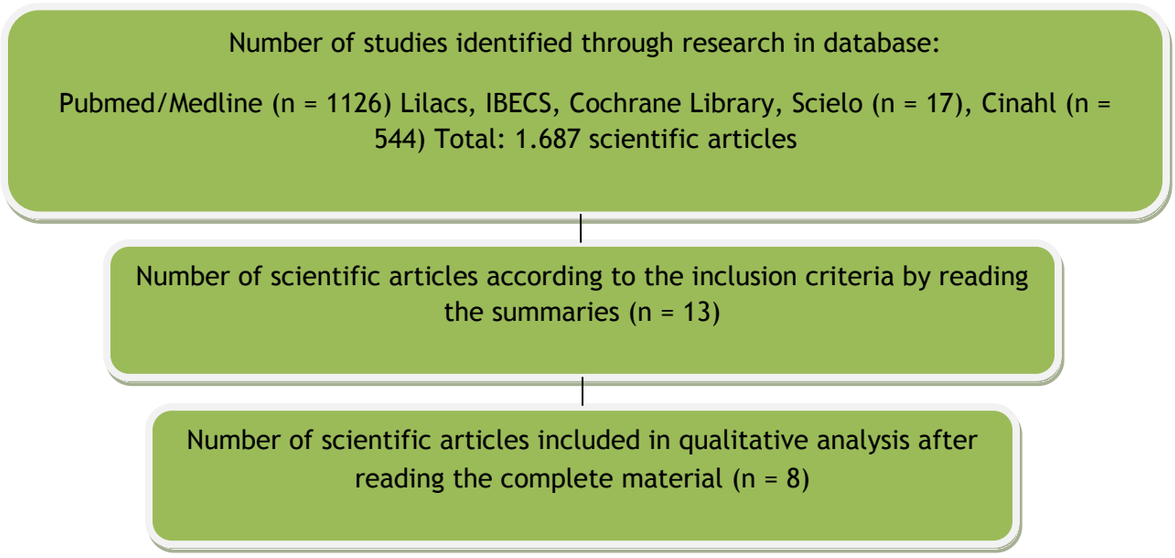

Figure 1. Flowchart of recovery studies in integrative review. Belo Horizonte, 2014.

The proposed interventions addressed the prevention and reduction of adverse effects caused by chemotherapy in patients with osteosarcoma.

The interventional therapies have been proposed in the analyzed studies, exclusively through drug therapy. The medications studied focused their intervention for prevention and control of toxicities related to

renal function, neurologic, cardiac, gastrointestinal and hematologic.

According to the methodological design of the articles, 12,5% are systematic review (with homogeneity) of case-control study for intervention in auditory toxicity; 37,5% used as a research methodology observation of therapeutic results, with 12,5% focused intervention in renal toxicity, 12,5% in the intervention for hepatic and hematologic toxicities and 12,5% for hepatic toxicity and leukocytosis; 50,0% are controlled and randomized clinical trials with narrow confidence interval, and 12,5% for intervention in renal, auditory and cardiac toxicity, 37,5% for emesis, as Figure 1:

Author	N	Year	Adverse Effect	Type of study	N.E.*	G.R.**
Jaffe et al.[17]	1°	1993	Hepatotoxicity and Leukocytosis	Observation of therapeutic results	2C	B
Widemann et al.[18]	2°	1997	Acute renal failure	Observation of therapeutic results	2C	B
Forni et al.[19]	3°	2000	Acute emesis	Randomized controlled trial with narrow confidence interval	1B	A
Forni et al.[20]	4°	2003	Acute emesis	Randomized controlled trial with narrow confidence interval	1B	A
Luisi et al. [21]	5°	2006	Nausea and vomiting	Randomized controlled trial with narrow confidence interval	1B	A
Grosso et al. [22]	6°	2006	Liver toxicity and hematologic	Observation of therapeutic results	2C	B
Castorena et al. [23]	7°	2007	Auditory and cardiac, renal toxicity	Randomized controlled trial with narrow confidence interval	1B	A
Van As JW, van den Berg H, van Dalen EC[24]	8°	2012	Ototoxicity	Systematic review (with homogeneity) of case-control studies	3A	B

Figure 1. Distribution of articles by author, year of publication, adverse effect observed, type of study, level of evidence and grade of recommendation. Belo Horizonte, 2014.
Legend: N.E.*: Level of Evidence, G.R**: Level of recommendation, N^0- Article number.

After analysis of scientific articles it can demonstrate interventions for impairments in gastrointestinal, renal, neurological, cardiac and hematological functions.

Author	Adverse effects	Age (in years)	Location of the tumor	QT	Interventions
Jaffe et al. [17]	Changes in liver function and leukocytes and erythrocytes	4 a 16	Not described	methotrexate	I-leucovorin versus d, I-leucovorin
Widemann et al. [18]	Nephrotoxicity	12 a 47	Not described	methotrexate	carboxypeptidase G2, thymidine, and leucovorin
Forni et al. [19]	Acute emesis	6 a 40	Extremity	cisplatin and ADRIAMYCIN ifosfamide	ondansetron, granisetron, and tropisetron
Forni et al. [20]	Acute emesis	9 a 45	Not described	cisplatin doxorubicin	tropisetron and dexamethasone
Luisi et al. [21]	Nausea and vomiting	0 a 20	Not described	ifofosfamida (2500 mg/m2) and epirrubicina (75 mg/m2) or carboplatin (600 mg/m2), or epirrubicina (75 mg/m2) and carboplatin (600 mg/m2)	ganisetron versus metoclopramia and dimenhydrinate
Grosso et al. [22]	Liver toxicity and hematologic	16 a 70	Not described	Trabectedin®	dexamethasone
Castorena et al. [23]	Cardiac toxicity auditory toxicity renal toxicity	7 a15	Not described	Cisplatin and doxorubicin	amifostine
Van As JW, Van den Berg H, Van Dalen EC [24]	auditory toxicity	0 to 22	Not described	Platinum	amifostine

Figure 2. Distribution of the studies according to authors, adverse effects, age range, location of tumor, chemotherapy and interventions used. Belo Horizonte, 2014.

• Interventions for impaired gastrointestinal function

The fourth scientific paper presented a sample of 32 patients, aged 9 to 45 years old diagnosed with osteosarcoma treated with continuous infusion of chemotherapy. Patients in the study were subjected to two cycles of chemotherapy: the first cycle was infused cisplatin (CDDP) 120 mg/48 m infusion, followed by doxorubicin (Doxo) 75mg/m in 24 hours; in the second cycle it was administered 15mg/m ifofosfamida (IFO) in 120 hours. The administration of dexamethasone and tropisetron at doses of 5 mg and 8 mg, respectively, at intervals of 12 hours, showed an anti-emetic efficacy in the control of vomiting, for the different cycles of chemotherapy. This effectiveness can be proven with a favorable response in 81,2% of patients using CDDP/Doxo and 79,3% for those receiving IFO. This protection was not continuous emesis in both cycles complete protection decreased from the first to the last day of treatment (256 days) from 100% to 62% during the first cycle and 100% to 63% during the second cycle.

The third study evaluated the antiemetic efficacy of ganisetron (2 mg/m²), ondansetron (5,3mg/ m²) and tropisetron (3,3 mg/m²) in a study of 90 patients with an average age of 16,9 years old. All patients were diagnosed end and osteosarcoma were treated with the following drugs: combination of Adriamycin (AD) 75 mg/m² 24-hour continuous infusion CDDP and 120 mg/m² 48-hour continuous infusion; and passed three weeks was administered IFO 15mg/m² in 120 hours of continuous infusion complete protection (CP) of vomiting was obtained in 59% of 717 days of treatment, without significant differences between the three drugs studied. The significantly higher rate of CP was obtained during chemotherapy with IFO (69%) compared with CDDP/AD (44%). The rate of PC decreased from the first to the last day of treatment, both for the CDDP/AD (61% to 27%) and for IFO (95% to 43%). When CDDP/AD and IFO were administered on various days by infusion granisetron, ondansetron and tropisetron has the same anti-emetic efficacy. One can show that the anti-emetic response to intervention applied during treatment had a decline of therapeutic effect to the development of chemotherapy.

The fifth study was conducted with 26 subjects, mean age 14 years, diagnosed with metastatic osteosarcoma or not undergoing chemotherapy in a day hospital. Being treated with chemotherapy: IFO 2,500 mg/m², epirubicin (EPI) 75 mg/m², carboplatin (CARBO) 600 mg/m², or EPI 75mg/m² associated with CARBO 600 mg/m². The patients received 50 mg/kg of granisetron administered in a single dose, 2 mg/kg associated with metoclopramide 5 mg/kg infusion dimenhydrinate 8 hours. Patients undergoing administration of granisetron obtained 62,5% complete response, absence of nausea and vomiting, and 10% achieved an effective response to metoclopramide plus dimenhydrinate.

The first study found that high doses of methotrexate (MTX) induces changes in liver function and aimed to evaluate the effectiveness of the I-leucovorin rescue methotrexate replacing d, I-leucovorin. The study included 9 patients aged 4 to 16 years old, with an established diagnosis of high-grade osteosarcoma with relapsed following treatment with MTX (12,5 g/m²). The scaled doses were 50mg and 100mg leucovorin I-d, I-leucovorin is administered every three hours until the serum concentration of MTX falls below 0,3µmol/l. Identified that half the dose of I-leucovorin was effective for the rescue of methotrexate compared d, I-leucovorin.

In the sixth article, we analyzed the infusion of the steroid dexamethasone in patients using chemotherapy trabectedin®. Study participants were 54 patients who underwent 202 cycles of chemotherapy, with disease refractory to other chemotherapy. Patients were adults and adolescents, aged between 18 and 70 years of age. The experimental group of the study consisted of 31 patients who received steroids the day before (dexamethasone, 8-20 mg iv) the administration of chemotherapy associated with routine antiemetics (ondansetron). Liver toxicity measured by transaminase (AST and ALT) had grade 3 and 4 toxicities in 70% of patients in the control group and in only 3% of patients in the experimental group. This data demonstrated the need for the prescription to be administered dexamethasone on the day prior to infusion of chemotherapy to control liver toxicity.

• Interventions for the impairment of neurological function

The seventh study was conducted with 28 patients, aged between 6-15 years old who received four cycles of cisplatin 150 mg/m² and intra-arterial dose of Doxo 75 mg/m² intravenously. The patients were randomized, and 15 patients received amifostine 740 mg/m² in 15 minutes by intravenous infusion, and 13 belonged to the control group. During the infusion of amifostine symptoms such as nausea, hypotension, and abdominal pain prevailed. 100% of ototoxicity grade 1 and 2

patients in the experimental group and 85% in the control group was observed. The study results showed that amifostine does not protect the patient against ototoxicity, which is triggered in patients taking high doses of CDDP.

The eighth article was a systematic review that looked at interventions induced by platinum-based chemotherapy (CDDP, CARBO, oxaliplatin) hearing loss. Patients included in the study were aged between 0 and 22 years old. The use of amifostine showed statistically significant results in three clinical studies. Two studies used amifostine at a dose of 740 mg/m² in 15 minutes by intravenous infusion immediately before the dose of platinum.[1] The study was conducted with 39 patients, two study with 82 patients. Another study used the same dose by intra-arterial infusion in 28 patients. This review concluded that there is no indication for the use of amifostine in control of auditory ototoxicity triggered by chemotherapy.

● Interventions for the impairment of cardiac function

The seventh study investigated the relationship of the administration of amifostine 740 mg/m² in 15 minutes by intravenous infusion to reduce cardiac toxicity. Of the 28 patients, two groups were listed, the experimental group of 15 patients and the control group with 13 patients. In the control group only 2 patients experienced cardiac toxicity grade 1, and the experimental group, there was no cardiac involvement due to the use of amifostine.

● Interventions for the impairment of renal function

The seventh article found that administration of amifostine 740 mg/m² in 15 minutes intravenous infusion is effective for reducing nephrotoxicity. It was noted that the toxicity was developed in 20% of patients who received amifostine and 30% in patients of the control group. One patient in the control group required to perform dialysis and died of relapse.

The second study evaluated the efficacy of three drugs in reducing renal toxicity induced by methotrexate. After reconstitution of carboxypeptidase G2 in normal saline, three doses of 50 U/kg were administered IV for 5 minutes at 4 hour intervals for the first six patients. The thymidine was administered 24 hours of continuous infusion at a dose of 8 g/m²/d. Finally, leucovorin was administered based on the plasma concentrations of methotrexate. Administration occurred in 20 patients with a mean of 16 years of age, with acute renal failure induced by high doses of methotrexate. Of these, 11 were diagnosed with osteosarcoma, 8 lymphoid cancer and 1 of gastric cancer. Carboxypeptidase G2 and thymidine were well tolerated, resulting in a rapid reduction of 95,6% to 99,6% in the concentration of methotrexate in plasma. The toxicity related to the use of methotrexate were mild to moderate, which leads to the conclusion that the use of carboxypeptidase G2, thymidine and leucovorin decreased risk of nephrotoxicity in the study patients.

● Interventions for the impairment of hematologic function

The sixth study recommends the administration of dexamethasone as premedication to decrease leukopenia and thrombocytopenia in patients undergoing treatment with trabectedin®. Leukopenia was observed in 24% of patients in the control group and in 2% of the experimental group ($p < 0,0001$). 25% of the control patients had thrombocytopenia, which was not observed in the experimental group

DISCUSSION

It was observed that for reducing the adverse effects of nausea and vomiting, dexamethasone and tropisetron administration in patients who are being treated with CDDP cycle, followed by Doxo and IFO cycle features very effectively at the beginning of the administration, however there is a decline the therapeutic effect throughout the treatment - NE:1B, GR:A.

Studies report that drugs granisetron, ondansetron and tropisetron are effective in reducing nausea and vomiting when administered to patients undergoing combination chemotherapy using AD/high doses of CDDP and IFO. However it is observed that the cycle IFO efficacy of granisetron, ondansetron and tropisetron are significant. Observe a decline in the effectiveness of both protocols from the first day of treatment - NE:1B, GR:A.

The reduction of nausea and vomiting can be effective with the administration of granisetron in patients treated with IFO, PPE, carboplatin, or carboplatin followed by EPI - NE: 1B, GR:A.

Was identified that half of the I-dose leucovorin is more effective in the rescue of MTX compared with the d, I-leucovorin - NE:2C, GR:B.

It was observed that the administration of corticosteroids dexamethasone in patients treated with chemotherapy trabectedin® is recommended, therefore, contributes to the control of liver toxicity - NE:2C, GR:B.

The administration of amifostine infusion is not recommended in patients under treatment with CDDP cycles of intra-arterial and intravenous Doxo. It is observed that patients who received amifostine had higher auditory toxicity when compared with patients who did not receive medication. Amifostine does not protect against hearing toxicity - NE: 1B, GR: A.

The study data are insufficient to be able to conclude the efficacy of amifostine in decreasing cardiac toxicity, whereas the cumulative dose of Doxo was relatively lower dose of 150 mg / m², considered less than a toxic dose of reference - NE: 1B,GR: A.

It was observed that no significant reduction of renal toxicity when using amifostine in patients being treated with CDDP intra-arterial and intravenous Doxo - NE: 1B, GR:A

It is recommended to administer dexamethasone prior to initiation of treatment with chemotherapeutic trabectedin® to the reduction of leukopenia and thrombocytopenia - NE: 2C, GR:B.

CONCLUSION

With this study it was found that the use of medications related to the infusion of chemotherapy aimed at children and adolescents with osteosarcoma, undergoing chemotherapy, adverse effects have been proven effective Importantly articles identified in this literature review also showed that certain medical therapies had not be effective in the management of signs and symptoms. It should be pointed out that interventions for adverse effects of administered anticancer medications in children and adolescents are not presented through non-pharmacological techniques, showing up as a gap in current scientific literature search.

Given the above, it is understood that there is a need for studies addressing the non-pharmacological treatment as an option to avoid those induced by the use of antineoplastic drugs in these patients' changes.

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