Management and Prevention of Adverse Reactions to Platinum Antineoplastic Chemotherapy in Patients with Esophageal and Gastric Cancer: Systematic Literature Review

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Manejo e Prevenção de Reações Adversas da Quimioterapia Antineoplásica com Platinas em Pacientes com Cânceres Esofágico e Gástrico: Revisão Sistemática da Literatura

Manejo y Prevención de Reacciones Adversas a la Quimioterapia Antineoplásica con Platino en Pacientes con Cánceres de Esófago y Gástrico: Revisión Sistemática de la Literatura

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ABSTRACT

Introduction: Gastric cancer is the fifth most common malignancy worldwide. It is the most frequent malignant tumor in Asia, especially in China. Esophageal carcinoma is one of the more aggressive types of malignant tumor. Multimodal treatments, including neoadjuvant chemotherapy and chemoradiotherapy are utilized and can cause fatigue, vomiting, diarrhea, skin changes, cachexia, and peripheral neuropathy, which can be important side effects for many patients undergoing their treatments. **Objective:** Carry out a systematic review on the management and prevention of adverse reactions of antineoplastic chemotherapy with platinum in patients with esophageal cancer and gastric tumor. **Method:** To select the articles, a search was conducted in three databases: MEDLINE/PubMed, Cochrane and Embase, with the PICO strategy, alternating between MeSH/DeCS descriptors and Boolean operators. **Results:** 455 titles were found, of which, after using the PRISMA guideline, 15 articles remained for systematic review, addressing the management and prevention of nausea and vomiting, peripheral neuropathy, cachexia, magnesium supplementation, treatment of depression and general toxicity. **Conclusion**: The greatest number of studies addressing the management and prevention of the symptoms of nausea, vomits, neuropathy and hypomagnesemia were found, and it was possible to identify some suggestions of conducts to treat these reactions. More studies are necessary for the other reactions encountered, mainly in the cases of gastric and esophageal cancer.

Key words: Stomach Neoplasms; Esophageal Neoplasms; Drug-Related Side Effects and Adverse Reactions; Platinum Compounds; Antineoplastic Agents.

RESUMO

Introdução: O câncer gástrico é a quinta doença maligna mais comum em todo o mundo. Trata-se do tumor maligno mais incidente na Ásia, especialmente na China. O carcinoma esofágico é um dos tipos mais agressivos de tumor maligno. Os tratamentos multimodais, incluindo quimioterapia neoadjuvante e quimiorradioterapia, são utilizados e podem causar fadiga, vômito, diarreia, alterações cutâneas, caquexia e neuropatia periférica, que podem ser efeitos colaterais importantes para muitos pacientes que realizam seus tratamentos. **Objetivo:** Realizar uma revisão sistemática sobre o manejo e a prevenção de reações adversas da quimioterapia antineoplásica com platinas em pacientes com câncer esofágico e tumor gástrico. **Método**: Para seleção dos artigos, foi realizada a busca em três bases de dados: MEDLINE/PubMed, Cochrane e Embase, com a estratégia PICO, variando os descritores MeSH/DeCS e operadores booleanos. **Resultados:** Foram encontrados 455 títulos, dos quais, após utilizar a diretriz PRISMA, restaram 15 artigos para a revisão sistemática, que abordavam o manejo e a prevenção de náusea e vômitos, neuropatia periférica, caquexia, suplementação de magnésio, tratamento de depressão e toxicidade geral. **Conclusão:** Verificou-se que náuseas, vômitos, neuropatia e hipomagnesemia tiveram maior número de estudos relacionados ao manejo e à prevenção desses sintomas, nos quais identificaram-se algumas sugestões de condutas com maior evidência para essas reações. As demais reações encontradas ainda carecem de mais estudos, principalmente nos casos de cânceres gástrico e esofágico.

Palavras-chave: Neoplasias Gástricas; Neoplasias Esofágicas; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Compostos de Platina; Antineoplásicos.

RESUMEN

Introducción: El cáncer gástrico es la quinta neoplasia maligna más común en todo el mundo. Es el tumor maligno más común en Asia, especialmente en China. El carcinoma de esófago es uno de los tipos de tumores malignos más agresivos. Se utilizan tratamientos multimodales, que incluyen quimioterapia neoadyuvante y quimiorradioterapia que pueden provocar: fatiga, vómitos, diarrea, alteraciones cutáneas, caquexia y neuropatía periférica, que pueden ser efectos secundarios importantes para muchos pacientes sometidos a sus tratamientos. **Objetivo:** Realizar una revisión sistemática sobre el manejo y prevención de reacciones adversas de la quimioterapia antineoplásica con platino en pacientes con cáncer de esófago y tumor gástrico. **Método:** Para la selección de los artículos se realizó una búsqueda en tres bases de datos: MEDLINE/PubMed, Cochrane y Embase, con la estrategia PICO, variando los descriptores MeSH/DeCS y operadores booleanos. **Resultados:** Se encontraron 455 títulos, de los cuales, luego de utilizar la guía PRISMA, quedaron 15 artículos para revisión sistemática, que abordaron el manejo y prevención de náuseas y vómitos, neuropatía periférica, caquexia, suplementación con magnesio, tratamiento de la depresión y toxicidad general. **Conclusión:** Se verifico que náuseas, vómitos, neuropatía e hipomagnesemia tuvieron un mayor número de estudios relacionados con el manejo y prevención de los síntomas, en los cuales fue posible identificar algunas sugerencias de conducta con mayor evidencia de estas reacciones. Las otras reacciones encontradas aún necesitan más estudios, especialmente en casos de cánceres gástrico y de esófago.

Palabras clave: Neoplasias Gástricas; Neoplasias Esofágicas; Efectos Colaterales y Reacciones Adversas Relacionados con Medicamentos; Compuestos de Platino; Antineoplásicos.

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INTRODUCTION

Gastric cancer is the fifth malignant disease most common worldwide, it is the most incident in Asia, especially in China. Great part of the cases is diagnosed as advanced gastric cancer at admission. Surgical resection complemented with post-operative chemotherapy continues as the primary treatment while post-operative recurrence is alarmingly high[1]. Esophageal carcinoma is one of the more aggressive types of malignant tumor. Multimodal treatments, including neoadjuvant chemotherapy and chemoradiotherapy improved the survival rate in patients with locally advanced esophageal carcinoma[2].

The systemic treatment of advanced metastatic esophageal cancer of gastroesophageal junction (GEJ) and of the gastric cancer utilizes a combination of multiple cytotoxic chemotherapeutic agents, although there is no standard regimen. Cisplatin and platinum agents are among the group of cytotoxic drugs more widely used and well succeeded in the whole world. Every year, more than 5.8 million patients are diagnosed with cancer for which first line therapy potentially includes platinum agents. The inclusion of high doses of cisplatin in radiotherapy exacerbates radiotherapy-associated adverse events and causes some specific platinum-related dose-dependent episodes. Nausea, vomits, ototoxicity, nephrotoxicity and neurotoxicity are noticed too with cisplatin treatment (monotherapy or in combination). In addition, these toxicities are cumulative, dose-dependent, many time irreversible (except nausea and vomits) and can involve extensive lesions in organs in regeneration or that do not regenerate and can impact the quality of life (QoL) of patients cured[3-5].

In Brazil, according to estimates of the National Cancer Institute José Alencar Gomes da Silva (INCA)[6], esophageal cancer is the sixth more frequent among men and the 15th in women and the eight more incident in the world. Gastric cancer is the third more common in men in the age range of 60-70 years old and the fifth in women. Protocols to prevent and manage the adverse drug reactions (ADR) of the platinum-based products are essential and an important subject for investigation. The National Comprehensive Cancer Network (NCCN)[7] guidelines for supportive care addressing the subject stand out, but so far, there are no systematic reviews consolidating the knowledge about management and prevention of neuropathy, nausea, vomit, nephrotoxicity, among other adverse reactions of specific diseases as esophageal and gastric cancers.

Based in this knowledge gap, the goal of this article was to review the literature addressing the management and prevention of antineoplastic chemotherapy adverse reactions with platinum in patients with esophageal and gastric cancers.

METHOD

Systematic review according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[8]. The study was registered at the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42020210705.

Studies with patients with gastric, esophageal, or gastroesophageal cancer were included (utilizing any criteria of acknowledged diagnosis). Studies addressing several types of cancer specifying the intervention (management or prevention) but not the disease were excluded.

Two reviewers conducted independently the search, firstly by reading the titles and abstracts following the inclusion and exclusion criteria. In a second moment, the articles were read fully, and the selection followed the eligibility criteria. The review included only observational and clinical trials, not gray literature. The eligibility of the articles was evaluated independently by two reviewers and discrepancies were resolved jointly by all the authors. The databases MEDLINE/PubMed, Embase and Cochrane Library addressing gastric cancer and esophageal cancer were searched, utilizing platinum-based products and systemic toxicities. Each database was researched fully, being eligible the studies of the last five years in any language in the months of July and August of 2020. The articles were selected in the databases mentioned according to the strategy PICO[9], varying the descriptors MeSH/DeCs and Boolean operators to apply the guidelines of PRISMA.

The same reviewers extracted the data independently utilizing a standard form based in the methodological characteristics of the studies, interventions and results, and discrepancies were resolved by consensus. The main results obtained addressed prevention and management of nausea and vomits, neuropathy, general toxicity, cachexia, nephropathy, and depression.

The risk of bias of the studies included was evaluated independently by the two reviewers pursuant to the following criteria: 1 – Identification of a clinical problem; 2 – Formulation of a relevant and specific clinical question; 3 – Search for scientific evidences; 4 – Evaluation of available evidences. For these questions, the information of Cochrane Effective Practice and Organization of Care[10] were utilized.

RESULTS

After the phase of identification of the articles in the databases, 455 titles were selected. Through PRISMA,

the selection was made for each stage (Figure 1). From the stage of identification to selection, 429 articles were excluded, including duplicates, abstracts, and scientific events. From the remaining 26 articles after application of the eligibility criteria, 15 articles were included after thorough analysis of the content of each title encountered in the eligibility stage. The total articles included in the systematic review represented 3% of the articles found in the databases.

Data collection was distributed in a spreadsheet according to the criteria of quality of Oxford evidence-based medicine[11] (Table 1) with the parameters: author, study design, number of patients, neoplasm, quality of the evidence.

According to the studies selected for review, some strategies of prevention or management of ADR were searched for. Each disease identified with its respective protocol was correlated with the type of ADR and the outcome of the intervention (Table 2).

The present review study tried to find scientific evidences about the management of the main adverse reactions caused by the treatment with platinum in gastric and esophageal cancer. It was possible to identify that the main findings were associated with *neuropathy, depression, cachexia, reactions of the gastrointestinal tract, mucositis, reduction of the levels of magnesium, nausea and vomits.*

Neuropathy

Three studies addressing neuropathy were identified, two for pharmacological treatments and one, non-pharmacological measures. The pharmacological studies show that the use of venlafaxine or duloxetine favors a better response in all levels of neuropathy. Despite N-acetylcysteine (NAC) had achieved favorable results against neuropathy, its efficacy needs more studies to prove it. The non-pharmacological study utilizing the method of whole-body vibration failed to show statistic difference in relation to the standard group[12-14].

Depression

A study about physical exercises and metabolism of kynurenine (Kyn) showed that it can improve depression in patients with cancer. The scores of depression and anxiety were obtained with the questionnaire HADS – Hospital Anxiety and Depression Scale in addition to the collection of biological specimens to check plasmatic concentrations of tryptophane (Trp), Kyn among other

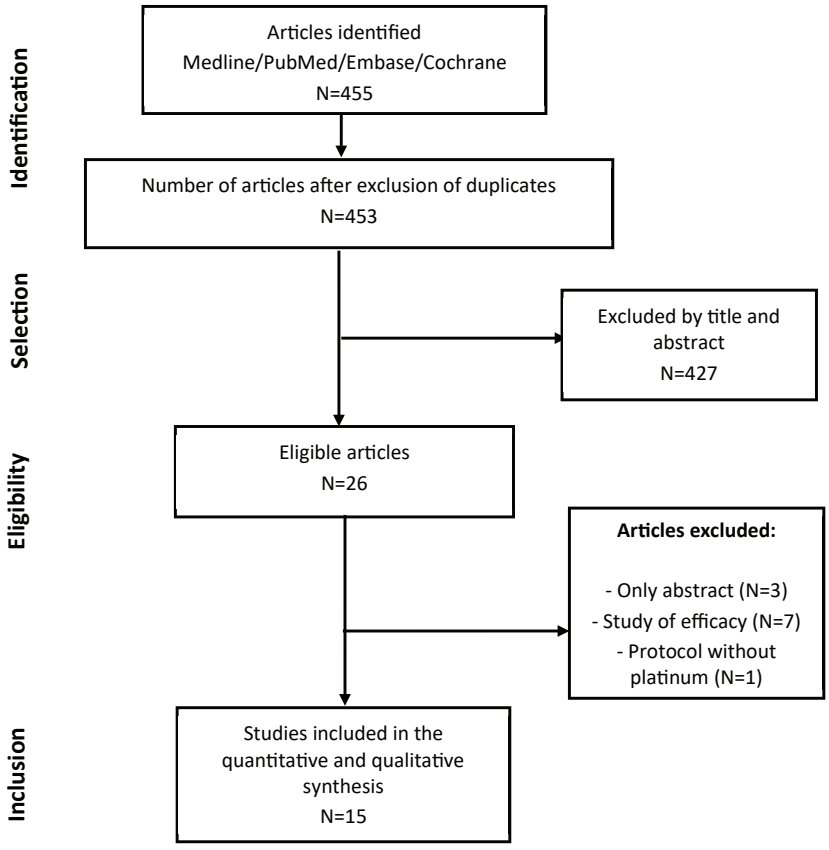

Figure 1. Flowchart of the process of selection of articles according to PRISMA

Table 1. Description of the articles selected

Author	Study design	Sample population (N)	Neoplasm	Quality of the evidence
Bondad et al.[12]	Double-blind, randomized clinical trial	32	Gastric cancer	A
Eltweri et al.[13]	Randomized, open, clinical trial	57	Gastroesophageal and gastric cancers	B
Farshchian et al.[14]	Double-blind clinical trial	156 (Esophageal cancer = 3)	Several types of cancer**	A
Hamai et al.[15]	Randomized, open clinical trial	18	Esophageal cancer	B
Herrstedt et al.[16]	Open clinical trial	43	Gastroesophageal	B
Kaidarova et al.[17]	Non-randomized, open clinical trial	127 (Gastric cancer = 49)	Gastric and lung cancer	B
Karthaus et al.[18]	Randomized, double-blind clinical trial	738 (Gastric cancer = 49)	Several types of cancer**	A
Khemissa et al.[19]	Randomized, double-blind clinical trial	201 (Gastric cancer = 17; esophageal cancer = 13)	Gastrointestinal cancer*	A
Konishi et al.[2]	Non-randomized, open, clinical trial	55	Esophageal cancer	B
Kouchaki et al.[20]	Randomized, double-blind clinical trial	90 (Gastric cancer = 47; esophageal cancer = 14)	Gastrointestinal cancer*	A
Schönsteiner et al.[21]	Randomized, open clinical trial	94 (Gastroesophageal cancer = 12)	Several types of cancer**	B
Schwartzberg et al.[22]	Randomized, double-blind clinical trial	404 (Gastric cancer = 24)	Several types of cancer**	A
Song et al.[23]	Randomized, double-blind clinical trial	83 (Gastric cancer = 13; esophageal cancer = 13)	Several types of cancer**	A
Tanaka et al.[24]	Non-randomized open clinical trial	14	Esophageal cancer	B
Yeganeh et al.[25]	Randomized, open clinical trial	62 (Gastric cancer = 24; esophageal cancer = 5)	Several types of cancer**	B

(*) Gastrointestinal cancer including gastric and/or esophageal cancer.
(**) Several types including gastric and/or esophageal cancer.

parameters. During the period of intervention, both groups presented significant reductions of the anxiety scores HADS[15].

Cachexia, reactions of the gastrointestinal tract, mucositis and myelosuppression

In a study comparing eligible patients who received megestrol plus placebo plus celecoxib randomly and the results of the beginning of the study, both groups revealed significant improvement, but the final evaluation showed that the addition of celecoxib to megestrol did not increase the anti-cachexia effects of megestrol[20].

Two clinical trials utilized nutritional compounds such as oncoxin (ONCX), glutamine, transformation growth factor beta 2 (TGF-β2) and polyunsaturated fat acids omega-3 (PUFA omega-3). ONCX was used with

Table 2. Strategies of prevention of chemotherapy adverse reactions

Author	Type of cancer/ protocol	Type of adverse reaction	Prevention/ Management	Outcome
Bondad et al.[12]	Gastric cancer XELOX	NP	Administration of two effervescent tablets of NAC 1,200 mg 1 hour before the administration of oxaliplatin for 8 cycles	Group treated with NAC presented NP in 68.8% vs.100% in control group
Schönsteiner et al.[21]	Gastic cancer and esophageal cancer Cisplatin-based protocols	NP	Stretching, passive mobilization, massage and WBV. Divided in 3 stages and according to tolerability. Interval of 15 days with 15 interventions in total	According to the chair standing test, the control group improved 56% vs. 68% of the test group (without statistic difference). For NP in the feet, there was better response in the test group in reducing the symptoms from 98% to 71% vs. 97% to 81% in control group (without statistical significance)
Farshchian et. al.[14]	Esophageal cancer FOLFOX Carboplatin TPF	NP	Daily administration of a tablet of venlafaxine 37.5 mg or duloxetine 30 mg	Reactions in highest grades - NCP - NP - NMP - SNP - NPA The group treated with venlafaxine vs. duloxetine vs. placebo presented NCP 21.6% (grade 2) vs. 11.8% (grade 2) vs. 31.4% (grade 2) respectively NMP 11.8% (grade 3) vs. 0% (grade 3) vs. 17.6% (grade 3) SNP 5.9% (grade 3) vs. 0% (grade 3) vs. 37.3% (grade 3) NPA 5.9% (grade 2) vs. 0% (grade 3) vs.11.8% (grade 3)
Herrstedt et al.[16]	Esophageal cancer EOX ECX CROSS	Depression	Aerobic physical and resistance exercises during 30 to 45 min per 12 weeks	Group treated with physical activity presented HADS scale of -1.33 [2.36; 0.31], p=0.01. Increased in 48% (p=0.001) with mean of concentration of 3-hydroxikynunerine, while in the exercise group (without HADS scale), the accumulation of this substance was attenuated

to be continued

Table 2. continuation

Author	Type of cancer/ protocol	Type of adverse reaction	Prevention/ Management	Outcome
Kaidarova et al.[17]	Gastric cancer XELOX Carboplatin + paclitaxel	Myelosuppression, hepatotoxicity, nephrotoxicity, hypoalbuminemia, asthenia, and depression	Food supplement consisting of amino-acids, vitamins, minerals, and oxidants 25 ml, twice a day for 20 days	Significant improvement of the quality of life. Mean, 2.07; CI 95%, 1.00-4.29). More elevated albumin in the test group (mean, 38.1; CI 95%, 37.1-39.1 g/l; vs. mean of the control group, 35.5; CI of 95%, 33.9-37.0; p=0.03
Tanaka et al.[24]	Esophageal cancer DCF	OM	Glutamine 8,832 mg/ day and ED 160 g. One week before and continuing after the beginning of chemotherapy	The incidence of grade ≥2 OM in the group concluding ED was lower, 15.4% vs. 66.7% (p=0.046) of those who did not conclude ED
Khemissa et al.[19]	Gastric cancer and esophageal cancer Cisplatin or oxaliplatin-based protocols	General toxicity (gastrointestinal, cutaneous, and neurologic)	150 g of food supplement containing approximately glutamine 13.5 g and TGF-β2 20 mg (Clinutren®). Two daily intakes (75 g each) and administered 5 days after the beginning of chemotherapy	Grades 3 and 4 non-hematologic and hematologic toxicities were not statistically different: 22.6% vs. 19.2% for non-hematologic toxicities and 17.7% vs. 15.2% for hematologic toxicities in control groups vs. test group
Eltweri et al.[13]	Gastroesophageal cancer EOX	General toxicity	Omega-3, 2 ml/Kg in 4 hours of infusion weekly	Nausea/vomit in test group vs. control group (0% vs. 19%, 260, p=0.04) Thromboembolic events, test group vs. control group (19% vs. 0%, p=0.04) Neutropenia grade 3 or 4 and test vs. control group (85% vs. 40%, p=0.002 and 60% vs. 16%, p<0.001)
Kouchaki et al.[20]	Gastric cancer and esophageal cancer FOLFOX XELOX DCF DOF	Cachexia	Megestrol 320 mg/day + celecoxib 200 mg/ day vs. megestrol 320 mg/day. Continuous use in the study phase	After two months, patients of Arm 1 (MA + placebo) and in arm 2 (MA + celecoxib) gained weight of 4.0 ± 3.4 and 2.2 ± 3.6 kg, respectively (p=0.163)
Konishi et al.[2]	Esophageal cancer DCF FP	Nephrotoxicity. Reduction of the glomerular filtration rate	Supplementation of IV Mg, 8 mg in DAY 1 of chemotherapy	Increase of the concentrations of creatinine post-chemotherapy without supplementation of Mg (p=0.01), with increase of grades 1 and 2 of 22.2% and 5.6%, respectively. After supplementation of Mg (alteration of creatinine, p=0.21), with increase of grades 1 and 2 of 8.1% and 0%, respectively

to be continued

Table 2. continuation

Author	Type of cancer/ protocol	Type of adverse reaction	Prevention/ Management	Outcome
Yeganeh et al.[25]	Gastric cancer and esophageal cancer Cisplatin-based protocols	Hypomagnesemia	Supplementation of oral Mg, 500 mg for each 50 mg/m² of cisplatin, divided in 2 or 3 daily intakes after the conclusion of each cycle, continuing until the next cycle and 2 to 3 weeks after the last cycle of chemotherapy	After follow-up, prevalence of hypomagnesemia in the intervention group was 10.7% vs. 23.1% in control group
Karthaus et al.[18]	Gastric cancer Cisplatin-based protocols	Nausea and vomit	Palonosetron oral, 0.5 mg vs. palonosetron IV, 0.25 mg. Dexamethasone 20 mg in D1, followed by dexamethasone 8 mg from D2 to D4 for both groups. Drugs were administered before and 24h after chemotherapy	Complete response rate in the acute phase was 89.4% for oral vs. 86.2% for IV. The non-inferiority interval was 3.21% (CI 99%)
Song et al.[23]	Gastric cancer and esophageal cancer Cisplatin-based protocols	Nausea and vomit	Thalidomide 100 mg, dexamethasone 4.5 mg and metoclopramide 10 mg, all oral from D1 to D5	Acute response to thalidomide in relation to control group (93% vs. 91%, p=0.767). Complete response rate was higher in the group of thalidomide during the general phase (75 % vs. 51%, p=0.024)
Hamai et al.[15]	Esophageal cancer Cisplatin-based protocols	Nausea and vomit	RKT, 7.5 g/day for 14 days starting in D1 of cisplatin. Associated with standard inhibitors of 5-HT3 and inhibitors of NK1 protocols and corticosteroids	The mean rate of food intake diminished between days 4 and 6 and was considerable low in the course with RKT than without it (2% vs. 30%, p=0.01, respectively)
Schwartzberg et al.[22]	Gastric cancer Cisplatin-based protocols and other alkylant agents	Nausea and vomit	NEPA: netupitant 300 mg and palonosetron 0.25 mg (NEPA oral), orally, 60 minutes before chemotherapy vs. fosnetupitant 235 mg and palonosetron 0.25 mg (NEPA IV), intravenous, 30 minutes before chemotherapy. Dexamethasone 12 mg in D1, followed by dexamethasone 8 mg from D2 to D4 before CT for both groups	Either IV or Oral NEPA the incidence of adverse events related to the treatment was similar in both groups (12.8% IV NEPA and 11.4% Oral NEPA during the whole study)

Captions: NP = Neuropathy; IV = Intravenous; O = oral; XELOX = Capecitabine/oxaliplatin; FOLFOX = Folinic acid/fluorouracil/oxaliplatin; TPF = Paclitaxel/cisplatin/fluorouracil; EOX = Epirubicin/oxaliplatin/capecitabine; ECX = Epirubicin/cisplatin/capecitabine; CROSS = Paclitaxel/carboplatin/radiotherapy; DCF = Docetaxel/cisplatin/fluorouracil; DOF = Docetaxel/oxaliplatin/fluorouracil; FP = Fluorouracil/cisplatin; ED = Elemental Diet; CT = Chemotherapy; RKT = Herbal Rikkunshito; vs. = Versus; NCP = Neuropathic cranial pain; NMP = Neuropathic motor pain; SNP = Sensory neuropathic pain ; NPA = Neuropathic pain; D = day; OM = Oral Mucositis; CI = Confidence Interval; WBV = Whole body vibration; HADS = Hospital Anxiety and Depression Scale; TGF-β2 = Transformation growth factor beta 2; Mg = Magnesium; NEPA = Netupitant/palonosetron; NAC = N-acetylcysteine; MA = Megestrol acetate.

the objective of improving the QoL by diminishing the side effects. Although the results obtained appear to be promising, more studies of multi-component nutritional supplements are necessary to explore opportunities to improve the QoL of the patients[26].

A phase II clinical trial about food supplement investigated the clinical, radiologic effects and of cytokines of intravenous infusion of PUFA omega-3. The most significant findings were reduced frequency of gastrointestinal and thromboembolic events. No benefit for survival was demonstrated for those treated with epirubicin/oxaliplatin/capecitabine (EOX) plus fish oil (PUFA omega-3). The authors concluded that this benefit in the response rate and reduction of chemotherapy-related gastrointestinal adverse events in EOX with or without fish oil should be evaluated by at least one phase II randomized study[19].

Finally, a study involving patients with stage II/III spinocellular carcinoma or esophageal adenocarcinoma followed the protocol docetaxel/cisplatin/fluorouracil (DCF). The authors concluded that an elemental diet (ED) can be one of the testing treatments to reduce the incidence of oral mucositis (OM) and should be evaluated in another randomized study[17].

Supplementation with magnesium

Two studies addressing magnesium supplementation (Mg) were identified, one intravenous and the other, oral. In the IV supplementation, Mg was administered in patients with esophageal spinocellular carcinoma treated with high dose cisplatin-based regimen and the protective effects of Mg supplementation against cisplatin-induced nephrotoxicity were reviewed prospectively in relation to the levels of parathormone (PTH) and parathormone-related protein (PTH-rP). No patient presented malnutrition or dehydration during the treatment[2].

In the study related to oral Mg supplementation, there was significant effect in the control group according to the dose of cisplatin contributing for the reduction of the decline of the levels of serum Mg after the six cycles of cisplatin-based chemotherapy[21].

Nausea and vomits

It was possible to identify four studies addressing the prevention of nausea and vomits in patients with esophageal and gastric cancer, two of them related to the use of inhibitors of serotonin 5-HT3 associated with inhibitors of neurokinins NK1[4,23], one related to the use of thalidomide and one, the herbal Rikkunshito (RKT)[22-24]. The results suggest satisfactory response profile against nausea and vomit as shown in Table 2.

DISCUSSION

The main ADR noticed in the studies were neuropathy, depression, nausea and vomits, hypomagnesemia, gastrointestinal toxicities, cachexia, and mucositis. The approaches these studies indicated involved pharmacological and non-pharmacological conducts.

Platinum products (oxaliplatin, cisplatin and carboplatin) are alkylant agents inhibiting the synthesis and replication of the DNA through crossed connections established by platinum compounds[4]. The ADR experienced by patients treated with antineoplastic drugs are similar, although the specific dose limiting toxicity (DLT) is different for each drug. For cisplatin, DLT is nephrotoxicity; for carboplatin, myelosuppression and for oxaliplatin, neurotoxicity[26].

Different mechanisms of neuropathy have been proposed for diverse classes of antineoplastics. Platinum products can reduce the axonal transportation and induce apoptosis of sensory neuron. In addition, experimental studies show the accumulation of platinum compounds in cellular bodies of dorsal root ganglia, diminishing the cellular metabolism and axonal transportation. Mitochondrial lesions appear to occur with the increase of the oxidative stress, which would induce chronic neuropathy[22].

In three studies with different treatment approaches to prevent neuropathies, 47 patients were evaluated, and the results indicated several responses according to the therapeutic conduct adopted. The study with the medications venlafaxine and duloxetine appear to present best evidences amidst the treatments applied. This clinical trial enrolled 156 individuals, of these, three patients with esophageal cancer. The overall results demonstrated that the effects of the reduction of motor neuropathy and neuropathic pain were better in the groups of duloxetine and venlafaxine. After four weeks, 23.5% of the patients for each one of these medications did not present symptoms of neurotoxicity and not anyone of the duloxetine group presented neuropathy grade 3[14]. The possible benefit of venlafaxine was suggested in a small placebo-controlled study with 48 patients with acute neuropathy by oxaliplatin. The group of venlafaxine had symptoms of relief compared with the placebo group (31% *versus* 5%), respectively. In another study with 231 patients, comparing the use of duloxetine with placebo, the relative risk of reduction of 30% of pain with duloxetine was 1.96 (CI95%=1.15-3.35) and reduction of 50% was 2.43 (CI95%=1.11-5.30), further to improving QoL as well[27].

In a study conducted by Bondad et al.[12], of a total of 32 patients, 16 were control group and 16 used NAC.

Despite positive results, 32.25% of the NAC group did not present neuropathy. The sensory electrophysiological results did not show significant difference between the two groups, control, and test. Studies for a prolonged period of use are recommended to confirm the potential of NAC[25].

Finalizing the series of neuropathy-related clinical trials, a study with 94 patients (12 with gastroesophageal cancer) evaluated the neurotoxicity with a non-drug therapy method, the WBV. The authors suggest that this program, compared with drug therapies, including antidepressants, anticonvulsants, antioxidant agents, neuroprotective drugs or medicinal plants can have objective response in neuropathies[13].

Depression is a comorbid disease in approximately 25% of all the patients with cancer. Individuals diagnosed with cancer undergo several layers of stress and emotional anguish, which may trigger it[28].

In a study with 43 patients with gastrointestinal cancer, the authors considered that, in 12 weeks of supervised exercises prior to the elective surgery it was possible to reduce the symptoms of depression in patients diagnosed with operable GEJ[20]. A randomized clinical trial with yoga in patients with breast cancer (n=88) corroborated the benefic effects of exercises in patients with cancer and indicated a potential explanation of exercises for depression. Both anxiety and depression can affect the treatment-related suffering, making patients aware that cancer is a threat needing additional attention to somatic symptoms and causing aversive symptoms[29].

All antineoplastic drugs including platinum-based present an array of severe side effects because of its low selectiveness for the carcinogenic tissue compared with the normal tissue by the high necessity of nutrients of the cancer cells. Although these drugs are absorbed by fast growth carcinogenic cells, they are also absorbed by other normal tissues that are growing rapidly[27].

In case of mucositis, it holds a relation with reactive oxygen species (ROS) compounds, which are the first conductors of damages to mucosa and represent a potential target to inhibit its development[30].

Overall, the studies involving glutamine in many associations are still contradictory, mainly in relation to mucositis. Four studies which enrolled 150 patients were identified with dietary supplementation. Of these, 44 patients used glutamine in two different studies to prevent OM and general toxicity. The first with 30 patients with gastric and esophageal cancers did not uphold the hypothesis that the addition of glutamine and TGF-β2 could prevent or reduce chemotherapy-related non-hematologic grade 3 and 4 toxicities in patients with gastrointestinal cancer. According to the author, so far, no randomized clinical trial was published about the effect of TGF-β2 in patients with cancer and the benefit of oral supplements of glutamine in these patients is still controversial. In addition, hematologic toxicities, treatment interruptions and inflammatory markers were not different among the two groups[18]. The administration of ROS eliminating compounds as glutamine provided contradictory evidences of its efficacy in preventing mucositis[30]. Some studies with few participants hamper the evaluation of OM, calling for other randomized studies and more participants for improved evidence[17,31].

A dietary supplementation with ONCX was utilized by 49 patients with gastric cancer and evaluated by investigators to reduce the toxicity of therapy associated with poor QoL. According to the findings, it was possible to detect that all the parameters related to the liver function (ALT and AST), to hemoglobin, emotional status, loss of appetite, physical condition and tiredness were lower in the group of medication in comparison with control group[16]. Vitamins regulating the route of metabolism of a carbon (pyridoxin, folate and cobalamin) play a crucial role in DNA stabilization and repair of structures. Together, these properties can be responsible for the efficacy of ONCX in reducing the symptoms of OM and improve the capacity of intaking solid food and maintain the body weight, in addition to controlling infectious complications and diminish the toxicity of the therapy in relation to leukocytes count and liver damages[32].

In a study with 57 patients with gastric and esophageal cancer addressing supplementation, PUFA omega-3 were utilized. The authors concluded that this benefit in the rate of response and reduction of chemotherapy-related adverse gastrointestinal events with protocol EOX with or without fish oil should be evaluated at least in a Phase II randomized study[19]. Another article of the same author reveals that PUFA, single DHA or in combination (Omegaven®), had the best effects *in vitro* than eicosapentaenoic acid (EPA) alone. The PUFA omega-3 are EPA and docosahexaenoic acid (DHA) that has anti-inflammatory effects and only a small quantity of these PUFA can be synthetized in the human body. In approximately 2-10% of α-linolenic, the acid is converted in EPA and DHA[33]. The PUFA are important components of the cellular membranes due to its fluidity. The molecules are substrates for the production of anti-inflammatory and inflammatory eicosanoids as exemplified by prostaglandins and leukotrienes. In cells of mammals, the fatty acids omega-6 and omega-3 compete for the metabolism by the same enzyme, producing acid arachidonic or EPA and DHA, respectively. EPA and DHA can replace the arachidonic acid in the cellular membranes and eliminate the production of pro-inflammatory mediators[34].

One of the important problems related to cancer is cachexia management. It affects the physical, psychologic, and social domains of life concomitantly. Thus, the QoL of patients with cachexia reduces drastically. The current evidence suggests that cachexia develops after a prolonged inflammatory response. The product is the catabolism of muscle proteins while the body tries to provide necessary elements for the synthesis of acute-phase proteins[35-37]. The results of a double-blind randomized study with 90 patients with gastrointestinal cancers (of these, 47 with gastric cancer and 14 with esophageal cancer) revealed significant improvement in the test group in relation to the beginning of the study among control and test groups, which made it different from some pilot-studies and clinical trials reporting encouraging results utilizing celecoxib or traditional anti-inflammatory for cachexia, but it was concluded that the results failed to show that the addition of celecoxib to megestrol increased the anti-cachexia effects of megestrol[20]. In a systematic review identifying 3,368 cancer patients (23% with gastrointestinal cancer), it was possible to notice that it was beneficial in relation to weight gain and increase of appetite in patients treated with single acetate of megestrol[38].

How platinum causes nephrotoxicity is not fully understood, but it is believed that it is because of direct and indirect damages to the kidneys. The main mechanism is attributed to acute tubular necrosis of the proximal tubular cells. Another effect, mainly cisplatin, is hypomagnesemia, which arises from the inability of the kidney to reabsorb Mg[26]. Two studies with 117 patients addressed the supplementation with Mg to avoid hypomagnesemia and the prevention of nephrotoxicity reactions. One of them was tested, although in small scale revealing that the intravenous supplementation of Mg ensured protective effects against cisplatin-induced nephrotoxicity; the other study with oral Mg suggested more investigations to establish a useful guideline for Mg supplementation in patients receiving cisplatin-based chemotherapy[25]. Studies indicate that for some patients, cisplatin can induce a defect in the renal tubular conservation of Mg that can result in severe clinical syndromes of Mg deficiency, being the supplementation of electrolytes a form of reducing the risk of nephrotoxicity after cisplatin-based chemotherapy[39].

Reactions of nausea and vomits are one of the main problems associated with the platinum-based protocols. Cisplatin is a highly emetogenic risk drug with more than 90% of the patients presenting nausea and vomits. In contrast, carboplatin and oxaliplatin are classified as moderate risk drugs with 30-89% rates of nausea and vomit. If the patients also receive platinum-based concomitant therapy, it can increase the incidence of chemotherapy-induced nausea and vomit (CINV). Although the treatment with antiemetic drugs is fairly well-succeeded, 10-30% of the patients still present nausea and vomits. Four studies were selected, one of them addressed the comparison between the antiemetic oral and intravenous palonosetron which had comparable safety profile without new concerns[18]. Both the combination of intravenous and oral netupitant and palonosetron (NEPA) had good responses in preventing CINV[40,41]. The lower-dose study with thalidomide did not increase the toxicity of the chemotherapy. However, the ideal low-dose of thalidomide to control CINV was uncertain[23,42]. Finally, with the herbal RKT no adverse event was reported, in addition to improving the QoL of patients with esophageal cancer[24]. The combination of one antagonist of receptors NK1, dexamethasone and a second antagonist of receptor 5-HT3 (5HT3RA) is currently considered the standard antiemetic treatment of patients receiving cisplatin-based chemotherapy. Palonosetron, a second generation 5HT3RA has shown to be superior for the prevention of acute and delayed vomits comparing with first generation 5HT3RA[43,44].

CONCLUSION

Based in the studies' contents described, it was possible to conclude that a great number of them addressed management and prevention of nausea and vomits, neuropathy and hypomagnesemia with suggestions of conducts grounded in strong evidences. More studies of proper prevention and management of depression, mucositis and cachexia are necessary, mainly in cases of gastric and esophageal cancer.

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Ney Moura Lemos Pereira contributed for the study conception or design, collection, analysis and/or interpretation of the data, wording and/or critical review with intellectual contribution. Telma Maria Araújo Moura Lemos and Fernanda Nervo Raffin contributed for the study conception and/or design, collection, analysis, and interpretation of the data. Rand Randall Martins and Roberto Fernandes da Costa contributed for the wording and/or critical review. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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