SOCIEDADE BRASILEIRA DE REUMATOLOGIA

REVISTA BRASILEIRA DE REUMATOLOGIA

www.reumatologia.com.br

Review article

Cyclophosphamide administration routine in autoimmune rheumatic diseases: a review☆

Kaian Amorim Teles[a,*], *Patricia Medeiros-Souza*[a,b,*], *Francisco Aires Correa Lima*[c], *Bruno Gedeon de Araújo*[d], *Rodrigo Aires Correa Lima*[e,f]

[a] *Universidade de Brasília (UnB), Departamento de Ciências da Saúde, Brasília, DF, Brazil*
[b] *Universidade Estadual de Campinas (Unicamp), Campinas, SP, Brazil*
[c] *Universidade de Brasília (UnB), Hospital Universitário de Brasília, Serviço de Reumatologia, Ambulatório de Colagenoses, Brasília, DF, Brazil*
[d] *Hospital Universitário de Brasília (HuB), Brasília, DF, Brazil*
[e] *Universidade de Brasília (UnB), Hospital Universitário de Brasília, Serviço de Reumatologia, Brasília, DF, Brazil*
[f] *Hospital de Base do Distrito Federal, Serviço de Reumatologia, Ambulatório de Artrite Reumatoide Inicial, Brasília, DF, Brazil*

ARTICLE INFO

Article history:
Received 2 August 2013
Accepted 7 April 2016
Available online 24 October 2016

Keywords:
Cyclophosphamide
Antiemetics
Chemotherapy
Cystitis

ABSTRACT

Cyclophosphamide is an alkylating agent widely used for the treatment of malignant neoplasia and which can be used in the treatment of multiple rheumatic diseases. Medication administration errors may lead to its reduced efficacy or increased drug toxicity. Many errors occur in the administration of injectable drugs. The present study aimed at structuring a routine for cyclophosphamide use, as well as creating a document with pharmacotherapeutic guidelines for the patient. The routine is schematized in three phases: pre-chemotherapy, administration of cyclophosphamide, and post-chemotherapy, taking into account the drugs to be administered before and after cyclophosphamide in order to prevent adverse effects, including nausea and hemorrhagic cystitis. Adverse reactions can alter laboratory tests; thus, this routine included clinical management for changes in white blood cells, platelets, neutrophils, and sodium, including cyclophosphamide dose adjustment in the case of kidney disease. Cyclophosphamide is responsible for other rare – but serious – side effects, for instance, hepatotoxicity, severe hyponatremia and heart failure. Other adverse reactions include hair loss, amenorrhea and menopause. In this routine, we also entered guidelines to post-chemotherapy patients. The compatibility of injectable drugs with the vehicle used has been described, as well as stability and infusion times. The routine aimed at the rational use of cyclophosphamide, with prevention of adverse events and relapse episodes, factors that may burden the health care system.

☆ Study conducted at the Serviço de Reumatologia, Hospital Universitário, Universidade de Brasília, Brasília, DF, Brazil.

* *Corresponding authors.*
E-mails: kaian.teles@gmail.com (K.A. Teles), pmedeirossouza@uol.com.br (P. Medeiros-Souza).

http://dx.doi.org/10.1016/j.rbre.2016.09.008

Rotina de administração de ciclofosfamida em doenças autoimunes reumáticas: uma revisão

Palavras-chave:
Ciclofosfamida
Antieméticos
Quimioterapia
Cistite

RESUMO

A ciclofosfamida é um agente alquilante vastamente usado para o tratamento de neoplasias malignas e pode ser usado no tratamento de diversas doenças reumatológicas. O erro de administração de medicamentos pode levar à diminuição da eficácia ou ao aumento da toxicidade medicamentosa. Diversos erros ocorrem na administração de medicamentos injetáveis. O trabalho objetivou a estruturação de uma rotina do uso de ciclofosfamida, bem como a criação de um documento de orientações farmacoterapêuticas para o paciente. A rotina foi esquematizada em três fases, a pré-quimioterapia, a administração da ciclofosfamida e a pós-quimioterapia, que levaram em consideração os medicamentos que devem ser administrados antes e depois da ciclofosfamida para prevenção aos efeitos adversos, incluindo náusea e cistite hemorrágica. As reações adversas podem alterar os exames laboratoriais e a rotina incluiu manejo clínico para alteração clínica dos leucócitos, das plaquetas, dos neutrófilos e do sódio incluindo o ajuste de dose de ciclofosfamida em caso de insuficiência renal. A ciclofosfamida é responsável por outras reações adversas raras, mas sérias, como hepatotoxicidade, hiponatremia severa e falência cardíaca. Outras reações adversas incluem perda de cabelo, amenorreia e menopausa. A rotina foi composta também por orientações ao paciente pós-quimioterapia. A compatibilidade dos medicamentos injetáveis com o veículo foi descrita, bem como o tempo de estabilidade e o tempo de infusão. A rotina visou ao uso racional da ciclofosfamida e prevenir os efeitos adversos e os episódios de recidiva, os quais podem onerar o sistema de saúde.

Introduction

Cyclophosphamide (CPM) is an alkylating agent widely used for the treatment of malignancies such as breast cancer,[1] multiple myeloma,[2] renal diseases including nephrotic syndrome refractory to corticosteroid and focal segmental glomerulonephritis, and this drug can be used in the treatment of multiple rheumatic diseases,[3–5] including cicatricial pemphigoid (also called pemphigoid mucous membrane),[4] rheumatoid arthritis,[5] juvenile dermatomyositis,[6] systemic sclerosis,[7,8] interstitial lung disease,[7] lupus vasculopathy,[9] systemic vasculitis, and refractory treatment of lupus-associated thrombocytopenic purpura.[10] In addition to other indications of cyclophosphamide, the treatment of neuromyelitis optica can also be included.[11]

In children, cyclophosphamide may be used in the treatment of nephrotic syndrome and systemic lupus erythematosus.[12,13]

Cyclophosphamide can be administered by oral or intravenous route.[14] The intravenous administration is more frequent in the field of rheumatology, taking into account studies showing an efficacy similar to that of oral treatment, but with less toxicity, for example, a decrease in premature ovarian failure, less severe infection, and lower overall exposure of the urinary tract to acrolein, a toxic metabolite of cyclophosphamide.[15] Cyclophosphamide is orally administered QD (24–24 h), while the intravenous route is administered in pulses, and the dose is adjusted according to hematologic and renal toxicities.[16]

The administration of cyclophosphamide in pulses may follow a weekly or monthly basis, in combination with a corticosteroid and other chemotherapeutic agents, provided that the attending physician takes into account the minimum blood count (NADIR) for the administration of cyclophosphamide.[16–18] Cyclophosphamide may cause some adverse events, and when these effects are related to the drug, are classified as an adverse drug reaction.[19] The adverse drug reaction can be conceptualized as an unintended and harmful reaction into the body, occurring in those routinely used doses in humans for prophylaxis, diagnosis, disease therapy, or for changes of physiological functions.[19]

A reaction that occurs in a small percentage of the population, but that, if not avoided, may cause irreversible damage to the patient, such as death, congenital abnormalities, birth defects or conditions that require permanent hospitalization, is classified as “severe reaction”.[19]

Some adverse reactions related to the administration of cyclophosphamide are bone marrow suppression, susceptibility to infections, sterility and amenorrhea,[18] as well as nephrotoxicity and cystitis,[18,19] and also cardiovascular complications, for instance, sinus bradycardia, pericarditis, myocarditis and heart failure.[20] Children and adolescents treated with high doses of cyclophosphamide are more likely to develop dental disorders and a decreased salivary flow. Cyclophosphamide is also teratogenic.[21] A long term reaction of cyclophosphamide is malignacies.[18] One can observe an increase in the incidence of bladder cancer and esophageal and lung adenocarcionoma, which customarily occur after two years of treatment.[18]

In addition to adverse drug reactions of cyclophosphamide, it is critical that the physician adopt all precautionary measures, because these adverse reactions may be more important in cases where cyclophosphamide is administered intravenously, given that, with this route of administration, the drug is not absorbed, the onset of its action is faster and, because the drug does not undergo first-pass metabolism, the bioavailability, i.e. the bioavailable concentration to exert a pharmacological action, becomes proportionally higher versus oral administration of cyclophosphamide.[22,23] Another important aspect to consider concerns the errors associated with the administration of injectable drugs.[24]

It is known that the use of injections is often associated with medication errors classified as serious events.[22] Intravenous-route administration errors represent 21.1% of all errors, with possible risk of errors of contamination, administration rate, and dilution.[25] Such parenteral drug administration errors, especially those by intravenous route, can cause an adverse drug reaction.[19]

In addition to health-related problems, it is required that the costs resulting from drug administration errors are taken into account. In Brazil, it is estimated that the annual cost with the use of chemotherapeutic drugs exceed 1.1 billion reais, and this value can increase in cases of injectable drug administration errors.[24]

Thus, one must bear in mind that these costs may be magnified by the occurrence of adverse events.[26] An adverse event is any untoward medical occurrence that affects the patient being medicated, but without a direct causal relationship with his/her treatment.[19]

Thus, it is important to standardize the administration of parenteral drugs and provide their rational use, which can be defined as the patient's need to receive the appropriate drug in the correct dosage for an adequate length of time and with the lowest cost.[27]

Taking into account the rational use of drugs, it is important to standardize rules for the parenteral administration of cyclophosphamide. The objectives of this study are proposing a cyclophosphamide administration routine in Rheumatology units, and the creation of a document containing pharmacotherapeutic guidelines for the patient, in order to maximize the efficiency of treatment based on a literature review.

Methods

Cyclophosphamide routine

An infusion routine for cyclophosphamide was developed in order to increase the bioavailability (effectiveness) of this drug while minimizing adverse reactions, thus rendering the treatment more tolerable for the patient. The protocol was divided into stages to facilitate the comprehension of the health staff and the replication of the cyclophosphamide dosing schedule. The drugs of the first (pre-ChT) and third (post-ChT) steps correspond to the administration of pharmaceuticals in order to prevent the main adverse reactions resulting from the administration of cyclophosphamide (second phase), including nausea, vomiting, and hemorrhagic cystitis. The clinical management of adverse reactions that change laboratory tests was described, as well as the clinical management of cyclophosphamide in renal failure. The rare, but serious, adverse reactions were also highlighted.

The most common adverse reactions were emphasized so that the attending physician could provide guidance with respect to the main care that the patient should take in his/her home, after administration of cyclophosphamide. These precautions are essential to prevent or minimize adverse effects and increase treatment adherence.

In addition, the compatibility of these injectable drugs with the vehicle, stability time, and infusion time was ascertained. The sequence of administration of these drugs has been prepared in order to increase the efficacy of cyclophosphamide and diminish the onset of adverse reactions to the drugs administered.

Results

The routine administration of cyclophosphamide was developed in three phases: pre-ChT, cyclophosphamide administration, and post-ChT. With a view to the prevention of hemorrhagic cystitis, intravenous hydration with a blood volume expander (a crystalloid: 0.9% saline) was standardized.[28] In addition, the drug administration sequence, the amount of diluent, the need (or otherwise) for dilution, infusion and administration times, and laboratory tests which should be monitored before and after the infusion of cyclophosphamide were indicated, as well as the guidelines to the patient.

Fig. 1 [3,5,20,29–42], lists the routine data, and Fig. 2 [44–50] describes the guidelines for the patient. Severe and uncommon adverse reactions which should be monitored are hepatotoxicity,[3] hyponatremia[45] (in this case, serum sodium level = 135 mmol/L [sodium is an univalent element; thus, 1 mmol/L = 1 mEq/L)],[45] and cardiovascular failure due to cyclophosphamide cardiotoxicity.[36]

Other adverse reactions from cyclophosphamide are amenorrhea,[18] early menopause,[46] and hair loss.[3]

Discussion

Drug administration errors can decrease the effectiveness of the pharmacological treatment and increase both the occurrence of adverse reactions and the financial costs of treatment.[24] A retrospective study conducted in hospitals in Spain between 2008 and 2010 evaluated the incidence of cost and adverse event. 245,320 episodes were identified, with an overall cost of 1,308,791.97 euros. Approximately 6.8% of patients experienced adverse events, representing a rise of 16.2% in costs. Six of the ten adverse events that burdened more significantly the hospital system occurred in the operating room, corresponding to an increase of expenses around 6.7% to the health system.[26]

A prospective study conducted between August and November 1999 and between January and May 2000 notified 1800 errors in 1663 patients. The number of notifications resulting from drug-related problems (including those probable and possible ones) was 215 (11.9%). Of these notifications, 108 (50.2%) were filled up due to adverse reactions, 100 (46.5%) came out of therapeutic failure related to dosing, and seven

Cyclophosphamide administration routine in autoimmune rheumatic diseases

Pre-chemotherapy administration scheme

Hydration with saline (S)
In the case of congestive heart failure, hypertension, acute/chronic kidney disease, use glucose solution. The infusion time must be 3h.

Specified dose: 1000 mL/S 0.9%[a] ☐	Dose: _____
Specified infusion: 1 hour/S 0.9%[a] ☐	Infusion time: _____
Specified time: 1 hour before cyclophosphamide ☐	Administration time: _____

Dexamethasone[b,c]

Specified dose: 20 mg ☐	Dose: _____
Dilution: 20 ml of S 0.9%[d] ☐	Dilution used: _____
Infusion: 10 minutes ☐	Infusion time: _____
Time: 1/2 hour prior to cyclophosphamide ☐	Administration time: _____

Mesna
The use of mesna is controversial; it may be replaced by a suitable hydration.[a]

Specified dose: 20% of the dose of cyclophosphamide[e] ☐	Dose: _____
Dilution: 20 ml of S[d] ☐	Dilution used: _____
Infusion: 15-30 minutes[e] ☐	Infusion time: _____
Time: 15 minutes prior to cyclophosphamide[e] ☐	Administration time: _____

The administration of cyclophosphamide is carried out immediately after pre-QT phase, with a dose between 0.5 and 1 g/m^2 body surface,[f,g] diluted into 100-200 ml saline,[h] with an infusion time of 60-120 minutes.[h]

Dosage scheme after chemotherapy

Furosemide[i]

Specified dose: 20 mg ☐	Dose: _____
Specified Infusion: 1-2 minute bolus ☐	Infusion time: _____
Specified time: immediately after cyclophosphamide ☐	Administration time: _____

Mesna
The use of mesna is controversial; it may be replaced by a suitable hydration.[a]

Specified dose: 20% of the dose of cyclophosphamide (IV) or 40% of the PO dose[e] ☐	Dose: _____
Dilution: 20 mL S in the case of IV[d] ☐	Dilution used: _____
Infusion: 15-30 minutes ☐	Infusion time: _____
Time: 4 and 8 hours for IV use, or 2 and 6 hours for PO[e] ☐	Administration time: _____

Ondansetron[j]

Specified dose: 8 to 16 mg (VO) ☐	Dose: _____
Time: 6 and 14h after cyclophosphamide ☐	Administration time: _____

Suggestion to interrupt cyclophosphamide treatment, according to hematological parameters

Platelets <100 000/mm^3 [k]
Absolute neutrophil count <1500 cells/μL [l]
White blood cell count <3500/mm^3 [k]

Precautions and clinical management of cyclophosphamide with respect to genitourinary system

Kidney failure - *clearance* <10 mL/min: Reduce the dose by 25%; supplementation with 50% after dialysis.[m]

Urinalysis - obtain a urinalysis every 4 weeks after administration of cyclophosphamide because of the risk of hemorrhagic cystitis;[n] watch for signs of hematuria, proteinuria, and leukocyturia.[o]

Noninvasive and invasive laboratory tests must be monitored in patients receiving cyclophosphamide according to the severity of their condition.

Noninvasive methods - echocardiography, assessment of cardiac function (systolic ejection and diastolic function, diastolic peak velocity and atrial and valve function, electrocardiograms, electrocardiography, 24-hour Holter ECG).
Invasive methods - magnetic resonance imaging, myocardial biopsy.[p]

Serious and uncommon adverse reactions should be monitored:
Hepatotoxicity[q] and hyponatremia. Serum sodium concentration in this case is 135 mmol/L (sodium is an univalent element; thus, 1 mmol/L=1 mEq/L).[r] Cardiovascular failure due to cyclophosphamide cardiotoxicity.
Other adverse reactions from cyclophosphamide:
Amenorrhea,[k] premature menopause,[g] and hair loss.[q]

Fig. 1 – Cyclophosphamide administration routine in autoimmune rheumatic diseases.
Sources: [a]Shepherd et al.[29]; [b]Hawthorn; [e]Cunningham[30]; [c]Jordan et al.[31]; [d]Turner et al.[32]; [e]Trissel[33]; [f]Haubitz et al.[34]; [g]Mardegan et al.[35]; [h]Di Lisi et al.[36]; [i]Salido et al.[37]; [j]Calixto-Lima et al.[38]; [k]Lotan et al.[20]; [l]Zahn et al.[39]; [m]Milman[40]; [n]Mota et al.[5]; [o]McDermid and Lönnerdal[41]; [p]Centro de Oncologia Unimed Birigui[42]; [q]Subramaniam et al.[3]; [r]Mota et al.[43]

Water intake - the physician should instruct the patient to drink at least two liters of water a day unless in the presence of a kidney condition; thus, the amount of water to be consumed should be individualized. Imprensa electrolytes in the blood.[a]
Instructions for preventing mucositis - cyclophosphamide can cause mucositis; some precautions are advisable and these should be taken by the patient to minimize risks, including brushing adequately his/her teeth after a meal, using a soft brush and a non-abrasive toothpaste (for children), avoiding alcohol and cigarettes, avoiding too much salt, choosing soft foods, giving preference to food in the form of puddings, porridges, vitamins, gelatin, and caloric-, protein-rich meat, chicken or fish soup.[b,c]
Clinical management for symptoms of nausea - the patient should eat before getting hungry, with small, frequent (2-2 hours), slowly eaten meals because hunger can increase nausea; also, should avoid very spicy, fatty and sweet food and hot food and drinks. On the other hand, the patient should avoid drinking liquids during meals and should stay away from the kitchen during food preparation, eating in a ventilated and pleasant environment.[b]
Guidelines for patients with anemia - the patient should consume foods of animal origin such as chicken, fish and especially red meat, and should consume legumes and dark green vegetables such as kale, broccoli and spinach, pea beans and other grains, and combine vegetables with sources of vitamin C (orange, mandarin [tangerine], lemon, acerola). Milk, cheese, cottage cheese, yogurt and other dairy products should be avoided during or close to lunch or dinner time.[d,e]
Guidelines for disposal of urine and faeces - on the appointed day to take cyclophosphamide and on the next two days, when using the toilet the patient should flush three times with the cover closed. If someone else is responsible for the cleaning of the patient's excreta, this person should wear gloves and use disposable material. The cleaning procedure must be done in a outside-inside manner; and all content should be placed in two plastic bags, which will then be tightly closed. Cleaning should be completed with bleach.[f,g]
Guidelines for bathing - the patient must first wash his/her hands, then the face and head. Next, the stomach, back, arms and the catheter (if in use of one of these devices).

Fig. 2 – Guidelines for the patient taking cyclophosphamide.
Sources: [a]Instituto Estadual de Hematologia Arthur de Siqueira[44]; [b]Bruining et al.[45]; [c]González et al.[46]; [d]Otero López[47]; [e]Medeiros-Souza et al.[48]; [f]Mesna[49]; [g]Taketomo et al.[50].

(3.3%) were due to intoxication. According to the criteria (modified) of Schumock and Tornton, 68.4% of drug-related problems are considered as preventable.[47]

The cyclophosphamide dosing schedule took into account the most common adverse reactions, the administration's strategy in the case of kidney failure, and the sequence in the administration of pre-ChT drugs, cyclophosphamide, and post-ChT drugs; to this end, the dosage of all medications used, their dilution and infusion time also were included.

The main clinical strategies in the face of adverse reactions from cyclophosphamide use included the care of hemorrhagic cystitis, nausea, and vomiting.[18] The administration of these drugs corresponds to what is defined as a qualitative polypharmacy, wherein the administration of a medication is performed to correct the adverse reaction of another medication.[48]

Several clinical strategies have been proposed to avoid hemorrhagic cystitis, including increased hydration of the patient and the administration of mesna and furosemide.[28,29] In those cases in which the patient suffers of a severe kidney impairment, it is preferable to administer mesna in place of hydration, due to the patient's water restriction.[20,29]

For the prevention of hemorrhagic cystitis, mesna is administered in a dose equivalent to 60% of cyclophosphamide, divided into three doses – 20% 15 min before the administration of cyclophosphamide, 20% after cyclophosphamide, and 20% 4 or 8 h after cyclophosphamide.[28] Mesna reduces the deposit of acrolein (a metabolite of cyclophosphamide) in the bladder, thus preventing hemorrhagic cystitis and bladder cancer.[18]

In order to decrease the exposure of the urinary tract to acrolein, the patient should be well hydrated before, during and after the administration of cyclophosphamide. Thus, at the time of his/her admission, the patient should receive, through a venous access, 1 L of a blood volume expander (a crystalloid: saline 0.9%) for 1 h, 60 min before the administration of cyclophosphamide.[51]

Cyclophosphamide per se can be administered at any time. In turn, the infusion of mesna depends on the administration of cyclophosphamide.[28] Mesna may be administered by oral or parenteral (subcutaneous or intravenous) route.[28]

The oral administration of mesna has the advantage of a convenient dosage schedule; however, its use brings some disadvantages, for instance, a higher frequency of nausea and vomiting.[49,50] Another limiting factor of the use of this drug orally is the decreased bioavailability versus parenteral route, due to first-pass metabolism, in addition to the potential decrease in its absorption as a result of frequent episodes of vomiting caused by the treatment with cyclophosphamide.[31] Taking into account the concepts that guide the rational use of pharmaceuticals, including the reduction of treatment costs for both the patient and society, oral administration of

mesna would have also the advantage of a likely decrease in expenses, due the lower bed occupancy time and less workload of the nursing team.[51] Still in this context, another possible disadvantage is the patient's non-compliance; thus, one cannot be sure that the patient has taken, or otherwise, the last dose of mesna PO.[52]

The advantage of the use IV mesna is that there is no need of absorption, and the onset of action of this drug is faster, compared with oral administration.[22,23,53] The disadvantage of the parenteral route is the greater risk of contamination, administration errors, less dosing convenience, and increase of the patient's hospital stay.[23,53]

However, mesna administration with a view to the prevention of hemorrhagic cystitis in patients using cyclophosphamide in therapeutic doses for rheumatic diseases is controversial; thus, mesna may be replaced by a suitable hydration with 6 L of water per day, plus a diuretic drug, or the use of hydration with a volume of 3 L/m^2 per day.[54]

Furosemide is administered after cyclophosphamide infusion at a dose of 20 mg, in order to stimulate diuresis that, in synergism with mesna, decreases the exposure of urothelium to the action of acrolein.[55] The maximum concentration of furosemide is 10 mg/mL administered in bolus, achieving a therapeutic concentration of 10 mg/mL per minute.[55] The second dose of mesna (20% of cyclophosphamide dose) is administered in the interval between 15 and 30 min after the administration of cyclophosphamide.[28]

Nausea and vomiting are considered as common adverse reactions in chemotherapy, and this also occurs with cyclophosphamide[31] which, in turn, participates of many chemotherapeutic regimens. In this case, a routine has been proposed for the treatment of rheumatic diseases. Nausea caused by the exclusive administration of cyclophosphamide (without a therapeutic scheme) is classified as a late-onset nausea.[56] Thus, ondansetron was not required to prevent this effect.[56] A decrease in effectiveness is another reason for not using ondansetron prior to cyclophosphamide.[57]

This reduction in efficacy occurs because ondansetron is an inhibitor of CYP2B.[58] This occurs because cyclophosphamide is a prodrug that must be activated by CYP2B, resulting in 4-hydroxycyclophosphamide and aldophosphamide. These metabolites are transported to the site of action, where they undergo spontaneous cleavage, producing phosphoramide mustard, responsible for the pharmacological effects of the drug.[58]

Moreover, dexamethasone was added prior to chemotherapy, as a prophylactic agent to anaphylactic shock and also as an antiemetic.[59] Preferably, dexamethasone should be administered so that its peak coincides with the peak of physiological corticosteroids, which normally occurs at 8 a.m. and 16 p.m.[58] A peak in dexamethasone plasma concentration occurs within 60 min, and its action begins in 30 min.[55,60] Thus, the administration of dexamethasone should be started in the morning, 30 min before the administration of cyclophosphamide, preferably at 7:30 a.m.[58]

After the emesis caused by cyclophosphamide was classified as a delayed-type,[56] and in view of the decrease of cyclophosphamide efficacy when ondansetron is administered prior to this chemotherapeutic agent, ondansetron (8 mg PO[31,61] administered at 6 and 14 or 8 and 16 h post-ChT, and with a maximum dose of 16 mg after chemotherapy, not exceeding 32 mg per day) was the last drug used for the prophylaxis of emesis caused by cyclophosphamide.[31]

Other important adverse effects of cyclophosphamide include hematologic toxicity,[18] kidney failure,[20] hyponatremia,[45,62] neurological impairment,[45] amenorrhea,[18] early menopause,[46] hair loss,[3] hepatotoxicity (rare),[3] and late-onset cancer.[18] The dose of cyclophosphamide for the treatment of systemic lupus erythematosus, including those patients with neuropsychiatric and/or hematologic disorders, with class IV lupus nephritis, and with other serious manifestations of systemic lupus erythematosus, is 0.5–1 g/m^2 IV monthly,[5,62] with dosage adjustment in patients with hematological toxicity and kidney failure.[20,63] Adverse hematologic reactions caused by cyclophosphamide are classified as serious, as they cause high morbidity.[19,64] NADIR is the minimum hematologic counting that must be observed to see if the patient may or may not embark on another chemotherapeutic cycle.[65] The main hematological tests include platelets, neutrophils, white blood cells and neutrophil counts. Neutropenia is defined as a decrease in absolute neutrophil count <1500 cells/μL.[65] The main causes of neutropenia include hematologic disorders, autoimmune diseases, infection, adverse drug reaction, chemotherapy, and radiotherapy.[65] Thrombocytopenia occurs when the platelet count is <100,000/mm^3.[65] In a patient with a platelet count <81,000/mm^3 concomitantly experiencing leukopenia, the treatment should be discontinued until the platelet count increase to 99,000/mm^3.[65] However, cyclophosphamide can be used in the treatment of refractory thrombocytopenic purpura, and in this case, among the hematologic disorders, thrombocytopenia, and microangiopathic hemolytic anemia are included. Leukopenia[10] is defined as a white cell count <3500/mm^3.[65]

Hepatotoxicity is an adverse reaction caused by cyclophosphamide that normally occurs at high doses.[3] When hepatotoxicity occurs at low doses, the reaction is classified as a rare, but serious, event.[19,64] Acute liver failure with low-dose cyclophosphamide (200 mg) was described in a case report of a male Chinese aged 48 years with progressive glomerulonephritis secondary to Wegener's granulomatosis, 24 h after the administration of cyclophosphamide.[3] The diagnosis of granulomatosis with polyangiitis was established by pathological examination and c-ANCA.[3] The patient was being treated with high-dose methylprednisolone, plasmapheresis, intermittent hemodialysis and low intravenous doses of cyclophosphamide.[3] Other factors that may be associated with hepatotoxicity have been excluded, including antifungals, HIV, and hepatitis B and C.[3] Alanine transaminase increased from 41 U/L to 336 U/L at the day of administration of 200 mg of cyclophosphamide; in the next day, a peak of 566 U/L was reached.[3] Two weeks later, the patient was treated with another pulse of 200 mg of cyclophosphamide (second dose), and the concentration of alanine transaminase reached 1253 U/L.[3] A liver biopsy was not possible, because the patient had a clotting disorder.[3] Another laboratory parameter to be monitored is sodium concentration. Hyponatremia is considered as an electrolyte disorder identified in clinical practice.[45] Although many cases are mild or relatively symptomatic, hyponatremia is regarded as a clinically important finding,

with high morbidity and mortality. Neurological symptoms of hyponatremia occur at sodium levels <125 mmol/L.[66] Among the complications of hyponatremia, one can mention central nervous system disorders such as seizures, and even a permanent damage to the central nervous system, and death.[66] Syndrome of inappropriate antidiuretic hormone secretion (SIADH) was described in a case report in which this syndrome was associated with the use of IV cyclophosphamide in a dose of 500–1000 mg/m^2, with a serum sodium level <120 mmol/L in a patient presenting neurological complications.[62]

Cyclophosphamide may also cause cardiotoxicity. Routinely, echocardiography, a noninvasive method, is used to monitor cardiovascular function in patients treated with immunosuppressants.[36] Other non-invasive methods most widely used are electrocardiography and 24-h (ECG) Holter monitoring.[36] Invasive methods such as scintigraphy, magnetic resonance imaging and cardiac biopsy are also procedures that can be used in cases of adverse reactions classified as serious.[36]

Other adverse reactions caused by cyclophosphamide include amenorrhea, menopause, and late-onset cancer, including esophageal, lung and bladder adenocarcinoma.[18,46] Cyclophosphamide was administered at a dose of 750–1000 mg/m^2 body surface in LUMINA (Lupus in minorities, nature versus nurture), a multicenter study performed including 567 women aged under 51 years.[46] A decrease in gonadal function was found, and gonadal failure was defined as the occurrence of amenorrhea for more than six months without a history of hysterectomy.[46] Cyclophosphamide has also been associated with teratogenicity.[18]

As to cyclophosphamide dose adjustment in patients with kidney failure, this is only done in severe cases, that is, with a creatinine clearance <10 mL/min. The therapeutic regimen of cyclophosphamide should be modified, its dose should be reduced by 25%, and supplemented with 50% after dialysis.[34]

The dilution of the drugs used in cyclophosphamide routine was carried out with the goal of maintaining the highest possible concentration of the drug in its non-ionized form.[58] Thus, two parameters were taken into account: drug compatibility with the vehicle (saline, dextrose or ringer lactate) and its stability time in the vehicle; preference was given to those drugs whose stability time was longer, in order to ensure a more effective treatment.[33]

When the drugs used have proved compatible and stable with the same vehicle, preference was given to the choice of the same vehicle, as this facilitates their administration by the nursing staff and prevents pharmacokinetic interaction, which would cause ionization of the drugs and a decrease in their efficacy.[67]

Another important aspect that should be addressed is the education of the patient on the treatment to what he/she is being submitted. A study in the city of Natal with 40 women diagnosed with systemic lupus erythematosus at the Hospital Onofre has shown that patients showing greater adherence were those who understood correctly the treatment and also the disease; thus, these women satisfactorily understood the adverse events and the clinical management, in order to minimize these adverse drug reactions.[68]

Publications on adverse events are important tools for drug safety monitoring after their release for marketing purposes by the health authorities of each country.[69] This review of medication administration intended to standardize the administration of cyclophosphamide by health professionals, in order to minimize the adverse events caused by drugs, the so-called adverse drug reaction.[19]

Conclusion

The routine was developed in order to increase the area under the curve (AUC) for cyclophosphamide, and to attain an appropriate clinical management to minimize the adverse drug reactions that, if not properly prevented, will cause damage to the patient, for instance, an increased prevalence of vomiting, and acrolein deposition in the bladder. The clinical management of adverse reactions that alter laboratory tests was described in order to guide the application of these tests. Adverse reactions, even being rare, were highlighted because these events can cause high morbidity. Thus, the rational use of cyclophosphamide increases the safety of the treatment and reduces the cost of administration of this chemotherapeutic agent, since our goal is to avoid error.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Burkard ME, Wisinski KB, Njiaju UO, Donohue S, Hegeman R, Stella A, et al. Feasibility of 4 cycles of docetaxel and cyclophosphamide every 14 days as an adjuvant regimen for breast cancer: a Wisconsin Oncology Network study. Clin Breast Cancer. 2014;14:205–11.
2. Huang BT, Tan Y, Zhao WH, Zeng QC, Li BS, Chen RL. How to determine bortezomib-based regimen for elderly patients with multiple myeloma: PAD versus CBd, an observational study. J Cancer Res Clin Oncol. 2014;140:303–9.
3. Subramaniam SR, Cader RA, Mohd R, Yen KW, Ghafor HA. Low-dose cyclophosphamide-induced acute hepatotoxicity. Am J Case Rep. 2013;14:345–9.
4. Munyangango EM, Le Roux-Villet C, Doan S, Pascal F, Soued I, Alexandre M, et al. Oral cyclophosphamide without corticosteroids to treat mucous membrane pemphigoid. Br J Dermatol. 2013;168:381–90.
5. Mota LM, Cruz BA, Brenol CV, Pereira IA, Rezende-Fronza LS, Bertolo MB, et al. Consenso 2012 da Sociedade Brasileira de Reumatologia para o tratamento da artrite reumatoide. Rev Bras Reumatol. 2012;52:152–74.
6. Rosa Neto NS, Goldenstein-Schainberg C. Dermatomiosite juvenil: revisão e atualização em patogênese e tratamento. Rev Bras Reumatol. 2010;503:299–312.
7. Broad K, Pope JE. The efficacy of treatment for systemic sclerosis interstitial lung disease: results from a meta-analysis. Med Sci Monit. 2010;16:RA187–90.
8. Appenzeller S, Sampaio-Barros PD, Samara AM, Marques Neto JF. Crise renal como manifestação inicial de esclerose sistêmica sine scleroderma. Rev Bras Reumatol. 2004;44:87–9.
9. Chu H, Wu LH, Song D, Yu F, Zhao MH. Noninflammatory necrotizing vasculopathy in lupus nephritis: a single-center experience. Lupus. 2014;23:20–30.
10. Campos LM, Spadoni MS, Michelin CM, Jesus AA, Carneiro JD, da Silva CA. Thrombotic thrombocytopenic purpura at

presentation of juvenile systemic lupus erythematosus patients. Rev Bras Reumatol. 2013;53:120–6.
11. Yaguchi H, Sakushima K, Takahashi I, Nishimura H, Yashima-Yamada M, Nakamura M, et al. Efficacy of intravenous cyclophosphamide therapy for neuromyelitis optica spectrum disorder. Intern Med. 2013;52:969–72.
12. Hobbs DJ, Barletta GM, Rajpal JS, Rajpal MN, Weismantel DP, Birmingham JD, et al. Severe paediatric systemic lupus erythematosus nephritis – a single-centre experience. Nephrol Dial Transplant. 2010;25:457–63.
13. Lehman TJ, Singh C, Ramanathan A, Alperin R, Adams A, Barinstein L, et al. Prolonged improvement of childhood onset systemic lupus erythematosus following systematic administration of rituximab and cyclophosphamide. Pediatri Rheumatol Online J. 2014;12:3.
14. Suarez-Almazor ME, Belseck E, Shea B, Wells G, Tugwell P. Cyclophosphamide for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2000:CD001157.
15. Cox PJ. Cyclophosphamide cystitis – identification of acrolein as the causative agent. Biochem Pharmacol. 1979;28: 2045–9.
16. Mavragani CP, Moutsopoulos HM. Lupus nephritis: current issues. Ann Rheum Dis. 2003;62:795–8.
17. Dupuis LL, Boodhan S, Holdsworth M, Robinson PD, Hain R, Portwine C, et al. Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients. Pediatr Blood Cancer. 2013;60: 1073–82.
18. Furst DE, Tseng CH, Clements PJ, Strange C, Tashkin DP, Roth MD, et al. Adverse events during the Scleroderma Lung Study. Am J Med. 2011;124:459–67.
19. US Department of Health and Human Services. Food and Drug Administration. Guidance for industry and investigators: safety reporting requirements for INDs and BA/BE Studies. MD: Silver Spring; 2012. p. 29. Available at: http://www.fda.gov/downloads/Drugs/. . ./Guidances/UCM227351.pdf [accessed 08.08.14].
20. Lotan E, Leader A, Lishner M, Gottfried M, Pereg D. Unrecognized renal insufficiency and chemotherapy associated adverse effects among breast cancer patients. Anticancer Drugs. 2012;23:991–5.
21. Hsieh SG, Hibbert S, Shaw P, Ahern V, Arora M. Association of cyclophosphamide use with dental developmental defects and salivary gland dysfunction in recipients of childhood antineoplastic therapy. Cancer. 2011;117:2219–27.
22. Andrade ED. Terapêutica medicamentosa em odontologia: procedimentos clínicos e uso de medicamentos nas principais situações da prática odontológica. São Paulo: Artes Médicas; 1998.
23. Fuchs FD, Wannamacher L. Farmacologia clínica: fundamentos da terapêutica racional. Rio de Janeiro: Guanabara Koogan; 1992.
24. Wannmacher L. Erros: evitar o evitável. Uso racional de medicmanetos: tema selecionados, vol. 2; 2005. p. 1–6. Available at: http://www.saudedireta.com.br/docsupload/1284734732novo_erro_medico.pdf [accessed 08.08.14].
25. Melo LR, Pedreira MLG. Erros de medicação em pediatria: análise da documentação de enfermagem no prontuário do paciente. Rev Bras Enferm. 2005;58:180–5.
26. Allué N, Chiarello P, Bernal Delgado E, Castells X, Giraldo P, Martínez N, et al. Impacto económico de los eventos adversos en los hospitales españoles a partir del Conjunto Mínimo Básico de Datos. Gac Sanit. 2014;28:48–54.
27. Medeiros EFF, Moraes CF, Karnikowski M, Nóbrega OT, Karnikowski MGdO. Intervenção interdisciplinar enquanto estratégia para o Uso Racional de Medicamentos em idosos. Ciênc Saúde Coletiva. 2011;16:3139–49.
28. Schuchter LM, Hensley ML, Meropol NJ, Winer EP. Update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology, Chemotherapy, and Radiotherapy. J Clin Oncol. 2002;20:2895–903.
29. Shepherd JD, Pringle LE, Barnett MJ, Klingemann HG, Reece DE, Phillips GL. Mesna versus hyperhydration for the prevention of cyclophosphamide-induced hemorrhagic cystitis in bone marrow transplantation. J Clin Oncol. 1991;9:2016–20.
30. Hawthorn J, Cunningham D. Dexamethasone can potentiate the anti-emetic action of a 5HT3 receptor antagonist on cyclophosphamide induced vomiting in the ferret. Br J Cancer. 1990;61:56–60.
31. Jordan K, Sippel C, Schmoll HJ. Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: past, present, and future recommendations. Oncologist. 2007;12:1143–50.
32. Turner N, Stewart J, Barnett F, White S. Syndrome of inappropriate anti-diuretic hormone secretion secondary to carboplatin after docetaxel-carboplatin-trastuzumab combination for early stage HER-2 positive breast cancer. Asia Pac J Clin Oncol. 2012;8:e9–11.
33. Trissel LA. Handbook on injectable drugs. 17th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2013.
34. Haubitz M, Bohnenstengel F, Brunkhorst R, Schwab M, Hofmann U, Busse D. Cyclophosphamide pharmacokinetics and dose requirements in patients with renal insufficiency. Kidney Int. 2002;61:1495–501.
35. Mardegan LC, Soledade C, Sachetto Z, Bertolo MB, Amstalden EMI, Sâmara AM, et al. Síndrome de Churg Strauss: uma vasculite rara. Rev Bras Reumatol. 2004;44:179–84.
36. Di Lisi D, Bonura F, Macaione F, Peritore A, Meschisi M, Cuttitta F, et al. Chemotherapy-induced cardiotoxicity: role of the tissue Doppler in the early diagnosis of left ventricular dysfunction. Anticancer Drugs. 2011;22:468–72.
37. Salido M, Macarron P, Hernandez-Garcia C, D'Cruz DP, Khamashta MA, Hughes GR. Water intoxication induced by low-dose cyclophosphamide in two patients with systemic lupus erythematosus. Lupus. 2003;12:636–9.
38. Calixto-Lima L, Martins de Andrade E, Gomes AP, Geller M, Siqueira-Batista R. Dietetic management in gastrointestinal complications from antimalignant chemotherapy. Nutr Hosp. 2012;27:65–75.
39. Zahn KL, Wong G, Bedrick EJ, Poston DG, Schroeder TM, Bauman JE. Relationship of protein and calorie intake to the severity of oral mucositis in patients with head and neck cancer receiving radiation therapy. Head Neck. 2012;34:655–62.
40. Milman N. Anemia – still a major health problem in many parts of the world! Ann Hematol. 2011;90:369–77.
41. McDermid JM, Lönnerdal B. Iron Adv Nutr. 2012;3:532–3.
42. Centro de Oncologia Unimed Birigui. Cuidados com o paciente em quimioterapia. Available at: http://www.unimedbirigui.net.br/oncologia/downloads/manual_cuidados_com_o_paciente_em_puimioterapia.pdf [acessed 08.08.14].
43. Mota DM, Silva MG, Sudo EC, Ortún V. Uso racional de medicamentos: uma abordagem econômica para tomada de decisões. Ciênc Saúde Coletiva. 2008;13 Suppl.:589–601.
44. Instituto Estadual de Hematologia Arthur de Siqueira Cavalcanti (Hemorio). Rio de Janeiro: Manual do paciente em quimioterapia; 2006. Available at: http://www.hemorio.rj.gov.br/Html/pdf/Manuais/quimioterapia.pdf [accessed 08.08.14].
45. Bruining DM, van Roon EN, de Graaf H, Hoogendoorn M. Cyclophosphamide-induced symptomatic hyponatraemia. Neth J Med. 2011;69:192–5.
46. González LA, Pons-Estel GJ, Zhang JS, McGwin G, Roseman J, Reveille JD, et al. Effect of age, menopause and

cyclophosphamide use on damage accrual in systemic lupus erythematosus patients from LUMINA, a multiethnic US cohort (LUMINA LXIII). Lupus. 2009;18:184–6.
47. Otero López MJ. Errores de medicación y gestión de riesgos. Rev Esp Salud Pública. 2003;77:527–40.
48. Medeiros-Souza P, Santos-Neto L, Kusano LTE, Pereira MG. Diagnosis and control of polypharmacy in the elderly. Rev Saúde Pública. 2007;41:1049–53.
49. Mesna. In: UpToDate Inc. [base de dados da Internet]. Waltham, (MA); 2013. Available at: http://www.uptodate.com [accessed 01.07.14]. Requer assinatura.
50. Taketomo CK, Hodding JH, Kraus DM. Pediatric dosage jandbook. Cleveland: Lexi-Comp Inc.; 1992.
51. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010;363:221–32.
52. Dewulf NL, Monteiro RA, Passos AD, Vieira EM, Troncon LE. Adesão ao tratamento medicamentoso em pacientes com doenças gastrintestinais crônicas acompanhados no ambulatório de um hospital universitário. Rev Bras Ciênc Farm. 2006;42:575–84.
53. Golan DE. Princípios de farmacologia: a base fisiopatológica da farmacoterapia. Rio de Janeiro: Guanabara Koogan; 2009.
54. Monach PA, Arnold LM, Merkel PA. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: a data-driven review. Arthritis Rheum. 2010;62:9–21.
55. Mesna: Tampa (FL): Gold Standard; 2014. Available at: http://www.clinicalpharmacology.com [accessed 08.08.14]. Requer assinatura.
56. Jeong SW, Cho JW, Hwang JS, Song JD, Shin S, Jang JY, et al. The antiemetic effect of a novel tropisetron patch in anticancer agents-induced kaolin pica model using rats. Environ Toxicol Pharmacol. 2005;20:167–74.
57. de Jonge ME, Huitema AD, van Dam SM, Rodenhuis S, Beijnen JH. Effects of co-medicated drugs on cyclophosphamide bioactivation in human liver microsomes. Anticancer Drugs. 2005;16:331–6.
58. Goodman L. Goodman & Gilman: as bases farmacológicas da terapêutica. Rio de Janeiro: McGraw-Hill; 2001.
59. Andrews PL, Sanger GJ. Nausea and the quest for the perfect anti-emetic. Eur Pharmacol. 2014;722:108–21.
60. Dexamethasone. In: UpToDate Inc. [base de dados da Internet]. Waltham, (MA); 2013. Available at: http://www.uptodate.com [accessed 01.07.14]. Requer assinatura.
61. Cagnoni PJ, Matthes S, Day TC, Bearman SI, Shpall EJ, Jones RB. Modification of the pharmacokinetics of high-dose cyclophosphamide and cisplatin. Bone Marrow Transplant. 1999;24:1–4.
62. Gilbar PJ, Richmond J, Wood J, Sullivan A. Syndrome of inappropriate antidiuretic hormone secretion induced by a single dose of oral cyclophosphamide. Ann Pharmacother. 2012;46:e23.
63. Abdul Rasool Hassan B, Yusoff ZB, Bin Othman S. Association of neutropenia onset and severity with chemotherapy regimens and schedules. Asian Pac J Cancer Prev. 2011;12:1425–8.
64. Vieira FP, Rediguieiri CF, Rediguieiri CF. A regulação de medicamentos no Brasil. Porto Alegre: Artmed; 2013. p. 672.
65. Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. J Clin Oncol. 2011;29:532–43.
66. Letmaier M, Painold A, Holl AK, Vergin H, Engel R, Konstantinidis A, et al. Hyponatraemia during psychopharmacological treatment: results of a drug surveillance programme. Int J Neuropsychopharmacol. 2012;15:739–48.
67. Brasil. Ministério da Saúde, Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Departamento de Assistência Farmacêutica e Insumos Estratégicos. Formulário terapêutico nacional 2010: Rename 2010. 2ª. ed. Brasília: Ministério da Saúde; 2010. Série B. Textos Básicos de Saúde.
68. Faria DA, Revoredo LS, Vilar MJ, Maia EM. Resilience and treatment adhesion in patients with systemic lupus erythematosus. Open Rheumatol J. 2014;8:1–8.
69. Kelly WN, Arellano FM, Barnes J, Bergman U, Edwards IR, Fernandez AM, et al. Guidelines for submitting adverse event reports for publication. Pharmacoepidemiol Drug Saf. 2007;16:581–7.