REV BRAS REUMATOL. 2016;xxx(xx):xxx–xxx

SOCIEDADE BRASILEIRA DE REUMATOLOGIA

REVISTA BRASILEIRA DE REUMATOLOGIA

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Review article

Cyclophosphamide administration routine in autoimmune rheumatic diseases: a review☆

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ARTICLE INFO

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

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.

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

Please cite this article in press as: Teles KA, et al. Cyclophosphamide administration routine in autoimmune rheumatic diseases: a review. Rev Bras Reumatol. 2016. 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]

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