THE USE OF CYCLOPHOSPHAMIDE IN THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

INTRODUCTION: Cyclophosphamide (CYC) is an agent used to treat neoplasms and autoimmune diseases. This study evaluates the efficacy of CYC in the treatment of systemic lupus erythematosus (SLE), analyzing possible adverse effects, including neoplastic events. **METHODOLOGY:** Systematic searches were conducted in the BVS, PubMed, SciELO, and LILACS databases using specific descriptors on the efficacy of cyclophosphamide in the treatment of SLE. Articles in English and Portuguese published between 2000 and 2023 were included, excluding theses, unpublished dissertations, duplicate articles, and articles published before 2000. **RESULTS AND DISCUSSION:** The search resulted in 143 studies, of which 14 were selected for analysis. Cyclophosphamide is widely used in the treatment of systemic lupus erythematosus (SLE), especially in severe cases such as lupus nephritis (LN). Studies demonstrate its efficacy in reducing disease activity and inducing remission. However, prolonged use can lead to significant adverse effects, including hematologic toxicity and neoplastic risks. High doses are associated with serious adverse events and an increased risk of cervical neoplasia. Strategies such as low-dose cyclophosphamide administration and combination with other immunosuppressants have shown similar efficacy with fewer side effects. **CONCLUSION:** CYC is effective in reducing SLE activity and decreasing the need for corticosteroids, with lower dose regimens presenting fewer adverse effects. Combination with rituximab may improve clinical outcomes in refractory cases, but prolonged toxicity requires close monitoring and dose adjustments.

Keywords: Cyclophosphamide; Efficacy; Systemic Lupus Erythematosus;

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune inflammatory disease characterized by a systemic pattern and the absence of a definitive cure. Its prevalence is especially high in women of reproductive age, between 20 and 40 years, and in regions with high sun exposure (BRAZILIAN SOCIETY OF RHEUMATOLOGY, 2011). The clinical presentation of SLE is variable, with intermittent episodes of remission and recurrence, and may include symptoms such as lupus nephritis, musculoskeletal disorders, vasculitis,

serositis, pneumonia, dermatological lesions, endocarditis, and neuropsychiatric manifestations (WALLACE; GLADMAN, 2022).

Cyclophosphamide (CYC) is an antineoplastic and immunomodulator widely used in the treatment of various neoplasms, auto , and autoimmune diseases, and some dermatological conditions. Classified as an oxazaphosphorine alkylating agent, CYC can be administered orally (PO) or intravenously (IV), with the route, dosage, and duration of treatment adjusted according to the pathology being treated. The use of CYC in the treatment of SLE is based on its ability to eliminate B and T cells and inhibit antibody production. The main form of cyclophosphamide elimination occurs through hepatic metabolism, with its bioactivation dependent on the enzymes CYP2B6, CYP3A4, and CYP2C9, which, when activated, can lead to adverse events (FERNANDES et al., 2008).

CYC is often combined with other therapeutic agents, including glucocorticoids, to optimize disease management (MACEDO et al., 2020). However, as an immunosuppressant, CYC can induce adverse effects, such as an increased risk of urinary tract infections and a higher prevalence of cervical tumors (FANOURIAKIS et al., 2020).

Therefore, the importance of this study is noteworthy, as it will evaluate the efficacy and adverse effects of CYC, one of the most widely used drugs as an alternative therapy, given its importance in everyday medical practice and as an alternative therapeutic option. The present study aims to analyze the use of CYC in the treatment of SLE manifestations and to evaluate the relationship between CYC use and the occurrence of neoplastic events.

METHOD

Data collection was performed through a systematic search of the following databases: Virtual Health Library (BVS), PubMed, Scientific Electronic Library Online (SciELO), and Latin American and Caribbean Health Sciences Literature (LILACS). These databases were selected due to their comprehensiveness and relevance in the field of health and medicine.

The following descriptors were used to perform the search: ("Efficacy") AND ("Cyclophosphamide")) AND ("Lupus Erythematosus, Systemic"). The inclusion criteria for article selection were: studies published in English or Portuguese, covering the period from 2000 to 2023, which discussed the use of cyclophosphamide in the treatment of SLE and its efficacy. The exclusion criteria included un s and dissertations, duplicate articles, and publications prior to 2000.

RESULTS AND DISCUSSION

Cyclophosphamide has been widely used in the treatment of SLE, and its efficacy in reducing disease activity is well documented, as observed in studies such as that by Lehman et al. (2000), where a prolonged regimen of cyclophosphamide therapy in children with NL resulted in a significant decrease in disease activity, without progression to chronicity, and with an excellent clinical response.

However, the therapeutic benefits of cyclophosphamide are offset by a variety of adverse reactions that can significantly impact patients' quality of life and limit treatment continuity. Zhang et al. (2014), in a multicenter study, compared low-dose and high-dose cyclophosphamide regimens, revealing that treatment with high doses is associated with a higher prevalence of adverse events, including gastrointestinal reactions (31.25% versus 17.39%), infections (22.27% versus 13.04%), myelosuppression (19.92% versus 9.68%), and alopecia (19.14% versus 13.44%).

Hematologic toxicity is one of the most concerning adverse reactions associated with prolonged use of cyclophosphamide. Gonzalez-Lopez et al. (2004) observed a higher incidence of serious side effects in patients treated with intravenous cyclophosphamide for SLE-associated pulmonary hypertension, while Cheng et al. (2022) explored the combination of belimumab with low-dose cyclophosphamide, demonstrating comparable efficacy with a more favorable safety profile.

In addition to hematologic adverse effects, prolonged use of cyclophosphamide is associated with neoplastic risks, particularly in relation to the development of cervical dysplasia and cervical intraepithelial neoplasia. Bateman et al. (2000) reported a significantly higher incidence of cervical dysplasia in patients treated with cyclophosphamide, suggesting that exposure to this drug may increase the risk of cellular changes that c ly progress to malignancies. Similarly, Ognenovski et al. (2004) identified a correlation between cumulative cyclophosphamide dose and increased risk of cervical intraepithelial neoplasia, with each 1 g increase in cyclophosphamide corresponding to a 13% increase in the risk of developing CIN ($P = 0.04$). These findings underscore the importance of continuous and rigorous surveillance for early detection of malignancies in patients undergoing prolonged treatment with cyclophosphamide.

Given the risks associated with cyclophosphamide use, there is growing interest in optimizing therapeutic regimens to minimize toxicity while maintaining efficacy. Zhang et al. (2014) demonstrated that a low-dose, short-interval (SILD) cyclophosphamide regimen may be as effective as high-dose regimens for inducing and maintaining remission in patients with lupus nephritis, with a significantly lower incidence of adverse events.

CONCLUSION

In conclusion, CYC remains an essential component in the treatment of severe SLE, but its administration should be carefully adjusted to balance therapeutic efficacy with potential toxicity risks. Reduced-dose strategies and short-interval regimens should be explored to optimize treatment. Future research should focus on identifying biomarkers that can predict treatment response, as well as evaluating new therapeutic combinations that may increase efficacy and reduce toxicity.

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