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Rituximab, fludarabine, and cyclophosphamide versus fludarabine and cyclophosphamide for treatment of chronic lymphocytic leukemia: A systematic review with meta-analysis

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Contents

Abstract

Background: Chronic lymphocytic leukemia (CLL) is a disease of the lymphoid system, in which the most common therapy is fludarabine plus cyclophosphamide (FC). The addition of rituximab to FC has been used, a combination known as FCR.
Objectives: To perform a systematic review with meta-analysis of clinical trials between 2000 and 2012 comparing FC and FCR in patients with CLL.

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Material and methods: Electronic databases were searched using keywords related to the objectives of this review. The outcomes examined were progression-free survival and complete remission.
Results: The progression-free survival and the overall survival showed significant difference between the two regimens, with complete remission being more frequent in FCR-treated patients (odds ratio = 2.58; 95% CI: 2.13–3.13). Patients treated with FCR showed significantly higher neutropenia and serious adverse reactions.
Conclusion: Despite the favorable results of the FCR regimen on outcomes including complete remission, progression-free survival, and overall survival, there is a lack of methodological rigor and appropriate analyses in many of these studies, and thus, there is a need for further studies examining the effect of rituximab in CLL patients.

Keywords: Chronic lymphocytic leukemia; Rituximab; Cyclophosphamide; Fludarabine; Meta-analysis

1. Introduction

Chronic lymphocytic leukemia (CLL) is a disease of the lymphoid system that is clonal in origin and characterized by the progressive and irreversible growth of mature deficient B-cells (especially CD5+ and CD23+) [1]. CLL is associated with a strong familial risk, and although the genetic basis of individual susceptibility has not yet been identified, there is evidence suggesting a common etiology with lymphoproliferative disorders of B-cells related to variations of the human leukocyte antigens [2].

CLL is usually an incidental finding, wherein up to 25% of patients may be asymptomatic at the time of diagnosis. The remaining patients may present a variety of clinical signs including peripheral lymphadenopathy, hepatosplenomegaly, cytopenia, and autoimmune anemia, in addition to systemic symptoms such as night sweats, weight loss, fatigue, pain in the lower limbs, dyspnea, and tachycardia [3].

Diagnosis of CLL is confirmed by the presence of a B-lymphocyte count greater than $5 \times 10^9\,L^{-1}$ with typical monoclonal and phenotypic immune characteristics in the peripheral blood, or even with a lesser count of monoclonal B-lymphocytes. The disease has an extremely varied course with duration as short as a few months (with rapid and progressive evolution and unfavorable prognosis) or as long as two decades [4].

CLL is a disease that requires therapeutic planning according to the clinical condition and the capacity of the patient to tolerate treatment-associated toxicities. Treatment for CLL has become highly personalized, requiring oncologists to have increasingly detailed knowledge about all therapeutic options available [5]. However, the only therapeutic option that results in a cure is an allogeneic bone marrow transplant. For several decades, monotherapy with alkylating agents such as cyclophosphamide and chlorambucil was the first choice of treatment, with the latter being regarded as the "gold standard" in the majority of specialized centers [6]; chlorambucil still remains useful in many cases, especially considering the low cost, easy-to-use posology, and possible oral administration. However, there are few reports of complete remission (CR) with chlorambucil; it is also known to have possible undesirable side effects such as cytopenia, myelodysplasia, and acute myeloid leukemia after long periods of treatment [7].

Since the 1980s, analogues of purines, either alone or combined, have been part of the treatment of CLL, in particular, fludarabine, pentostatin, and cladribine [8,9], with fludarabine being the compound most studied and most often used. Fludarabine monotherapy has been shown to be satisfactory in some clinical trials [10,11] where higher rates of a "global" response were observed, in addition to higher remission rates when compared with other treatments containing alkylating agents alone or in combination with corticosteroids, but without improvement in overall survival (OS) when used alone [12]. The fludarabine-cyclophosphamide (FC) regimen has achieved good results with reports of responses higher than 86%, with CR rates over 23% and progression-free survival (PFS) of approximately 32 months [10–13].

Recently, the use of monoclonal antibodies directed against CD20, CD23, CD37, CD38, and CD40 antigens has been employed in the treatment of CLL. One such agent is rituximab [5,14–16] – a chimeric monoclonal antibody directed against CD20 [5] – that is widely indicated for the treatment of B-lymphocyte non-Hodgkin's lymphoma, and more recently, it was released by the Food and Drug Administration for use in CLL; in fact, it is considered first-line therapy in the treatment of this disease [17]. The FC regimen has been proposed for use in association with rituximab (a combination called FCR). However, the controversial results, high cost, and potentially serious and frequent side effects have contributed to its limited use in Brazil.

Considering the above, this systematic review with meta-analysis aims to comparatively evaluate the effectiveness and safety of FC and FCR regimens with the intention of providing assistance in clinical decision-making and healthcare management.

2. Material and methods

We performed a systematic review with meta-analysis, using the standard guidelines of the Cochrane Collaboration [18] and QUOROM [19], for comparing the effects of FC with FCR in the treatment of CLL.