Alkylating Agents in the Treatment of Waldenström Macroglobulinemia

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KEYWORDS

• Alkylating agents • Waldenström macroglobulinemia • DRC • CHOP
• Bendamustine

KEY POINTS

- Chemotherapy in combination with rituximab is still a key treatment element in Waldenström macroglobulinemia (WM).
- Among chemotherapeutics, alkylating agents are still widely used in WM.
- The combination of dexamethasone, cyclophosphamide, and rituximab is a highly active treatment option with a favorable toxicity profile.
- Future studies must define the role of alkylating agents in the treatment of WM in the era of emerging chemotherapy-free targeted therapies.

INTRODUCTION

In recent years, the emergence of ibrutinib has dramatically changed the treatment landscape of Waldenström macroglobulinemia (WM), underlining that chemotherapy-free therapy has an immense potential in this disease. In fact, ibrutinib is the most powerful single agent in WM treatment.[1] However, ibrutinib treatment has its limitations and challenges. There is genotype-dependent sensitivity toward ibrutinib with inferior response rates in patients with mutations of CXCR4 or wildtype MYD88 and wildtype CXCR4 genes.[2] In addition, ibrutinib has to be given until progression and, therefore, is a permanent therapy, causing substantial treatment costs. Furthermore, in Europe, ibrutinib is only approved in patients not eligible for chemoimmunotherapy. Based on all this, chemotherapy in combination with rituximab is still a cornerstone in the treatment of WM, reflected by recommendations in international and national guidelines.[3,4] Among the different chemotherapeutics, alkylating agents are the most important, particularly when bendamustine, which carries the characteristics of both an alkyl and a purine analogue, is added. Purine analogues, such as

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fludarabine, are highly efficient drugs in WM but have lost popularity because they can induce considerable toxicity by immunosuppression and myelotoxicity.[5] This article summarizes treatment outcomes for alkylating agents in WM.

RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISONE

Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) was developed more than 40 years ago and is still the backbone of treatment of different lymphoma entities, such as diffuse large cell lymphoma or follicular lymphoma. In WM, this combination regimen is highly effective, as documented in independent prospective trials. In a prospective randomized trial, the German Low-Grade Lymphoma Study Group could demonstrate that R-CHOP is a well-tolerated and effective treatment for first-line treatment of WM.[6] In the study, 48 WM subjects were randomly assigned to R-CHOP (n = 23) or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (n = 25). In the R-CHOP arm, a significantly higher overall response rate (ORR) of 91% versus 60% for CHOP alone was observed (P = .0188), whereas the complete remission (CR) rates were not statistically different (9% vs 4%; P = .60). R-CHOP led to a significantly longer time-to-treatment failure, with a median 63 months for R-CHOP versus 22 months in the CHOP arm (P = .0241) (Fig. 1). The Eastern Cooperative Oncology Group trial reported about its experience with the R-CHOP combination in the same setting: 91% of the subjects achieved objective response (PR) with a rapid median time to response of 1.6 months; at that time, with a median follow-up time of 18.3 months, median duration of response (DR) had not been reached. Myelosuppression was the main toxicity.[7] These studies indicate that combinations of rituximab with CHOP are highly effective and well-tolerated in medically fit patients. In particular, younger patients, in whom stem cell collection for later myeloablative treatment approaches is considered, R-CHOP is an excellent regimen. However, in many patients, particularly the elderly, R-CHOP is considered too toxic because of its myelosuppressive effects. Also, there is concern about applying neurotoxic vincristine to patients suffering from a disease that often causes neuropathy.

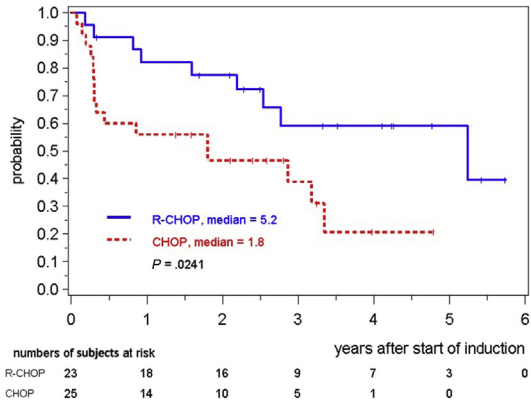

Fig. 1. Time-to-treatment failure after R-CHOP versus CHOP for subjects with treatment-naïve WM. (*Adapted from* Buske C, Hoster E, Dreyling M, et al. The addition of rituximab to front-line therapy with CHOP (R-CHOP) results in a higher response rate and longer time to treatment failure in patients with lymphoplasmacytic lymphoma: results of a randomized trial of the German Low-Grade Lymphoma Study Group (GLSG). Leukemia 2009;23(1):158; with permission.)