Frontline Management of Waldenström Macroglobulinemia with Chemoimmunotherapy

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KEYWORDS

• IgM lymphoplasmacytic lymphoma • Alkylating agents • Purine analogs
• Monoclonal antibodies • Limited-duration treatment

KEY POINTS

- Chemoimmunotherapy is a valuable and effective frontline approach for the management of patients with Waldenström macroglobulinemia.
- Alkylator-based chemotherapy with rituximab, especially bendamustine and rituximab doublet is highly active and commonly used in the treatment of Waldenstrom macroglobulinemia.
- The outcome of patients with Waldenström macroglobulinemia receiving chemoimmunotherapy is independent of their MYD88 mutation status.
- The finite duration of chemoimmunotherapy is particularly appealing to patients, given that the majority of toxicities resolve with completion of treatment.

INTRODUCTION

Waldenström Macroglobulinemia (WM) is a B-cell, IgM-secreting lymphoplasmacytic lymphoma (LPL), with an incidence of 1500–2000 new cases per year in the United States.[1–3] The median age at presentation is approximately 70 years and the disease is predominantly encountered among Caucasians. Despite remarkable advances in the field, WM remains incurable, with no benefit of early therapeutic intervention among the asymptomatic, incidentally diagnosed patients, without indications to treat. Moreover, patients with smoldering WM, managed with active surveillance alone, show comparable survival to the age- and sex-matched general population.[4] Therefore, in the absence of data supporting the benefit of early use of WM-directed therapy,

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intervention is best reserved for patients with active disease exhibiting unrelenting symptoms or significant cytopenias attributable to underlying WM. As curative therapies are lacking, palliation of symptoms, with disease control, and preservation of the quality of life have become overarching goals of the management of WM. When the patients with WM meet the indications for treatment, outside of clinical trials, they are typically offered one of the 3 approaches (i) fixed-duration chemoimmunotherapy (CIT), (ii) fixed-duration proteasome-inhibitor (PI)-based approach, or (iii) Bruton tyrosine kinase (BTK)-inhibitor-based treatment given continuously until progression or intolerable treatment-emergent toxicity. This review focuses on the CIT-based approaches for patients with previously untreated WM.

The preponderance of evidence in WM that has shaped our current approach was gathered either from subset analyses exclusively focused on WM patients within the larger randomized controlled trials of indolent lymphomas, or single-arm phase 2 trials and retrospective studies focussing on patients with WM. For a long time, limited-duration chemotherapy has been the linchpin of managing symptomatic WM. With the recognition of the merits of integrating anti-CD20 monoclonal antibodies into the existing chemotherapy backbones, CIT became a widely adopted strategy. Over time, as evidence from the use of CIT accumulated (Fig. 1), clinicians became more adept at managing this rare non-Hodgkin lymphoma. Fixed-duration anti-CD20 plus PI-based combinations have also been developed, but did not supplant CIT, probably due to the high rates of PI-associated neurotoxicity, particularly with bortezomib, among patients with WM. More recently, continuous BTKi-based therapies have offered an alternative approach to CIT although randomized trials comparing the 2 vastly different strategies remain absent.

Rituximab is a chimeric anti-CD20 monoclonal antibody with substantial clinical activity in WM, a malignancy with variable CD20 expression. Single-agent response

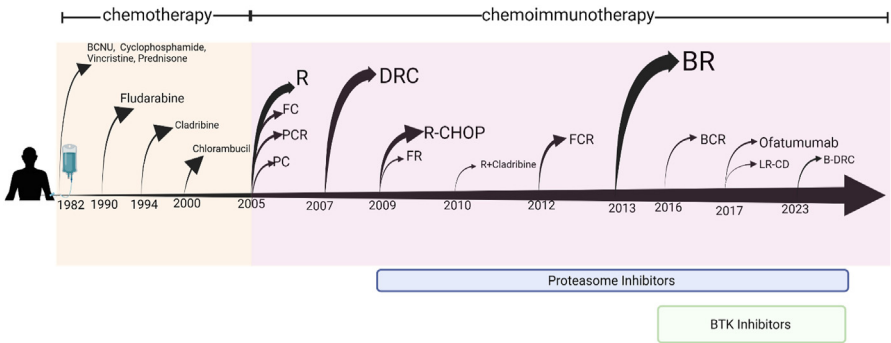

Fig. 1. Evolution of Chemoimmunotherapy in Waldenström Macroglobulinemia. The font sizes and the arrow width depict the impact of the respective regimens in the frontline setting. The time points on the horizontal axis represent the year of the publication of the initial clinical trial(s) with the specific regimens. The horizontal bars at the bottom show the time interval during which other classes of frequently used agents were developed and continue to be used in WM. Created with BioRender.com. BCNU, carmustine; BCR, bortezomib, cyclophosphamide, and dexamethasone; B-DRC, bortezomib, dexamethasone, rituximab, and cyclophosphamide; BR, bendamustine, and rituximab; BTK, Bruton's tyrosine kinase; DRC, dexamethasone, rituximab, and cyclophosphamide; FC, fludarabine, and cyclophosphamide; FCR, fludarabine, cyclophosphamide, and rituximab; FR, fludarabine and rituximab; LR-CD, lenalidomide, rituximab, cyclophosphamide, and dexamethasone; PC, pentostatin, and cyclophosphamide; PCR, pentostatin, cyclophosphamide, and rituximab; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

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rates of 30% to 50% have been observed in patients with treatment naïve WM.[5] Ofatumumab, another anti-CD20 monoclonal antibody, targets a different epitope of CD20 surface antigen and has more potent complement-dependent cytotoxicity than its predecessor, rituximab. As it is a fully human antibody, it is often used for patients who are rituximab intolerant, although scant prospective data support this approach. In a single-arm phase 2 trial, ofatumumab monotherapy has led to an overall response rate (ORR) of 67% among previously untreated WM (n = 9), with somewhat lower rates of IgM flare compared with rituximab.[6] In cross-trial comparisons, combination CIT regimens, for example, bendamustine or cyclophosphamide and anti-CD20 antibody, have shown superior disease control compared with anti-CD20 monotherapy, albeit at the cost of increased toxicity.

ALKYLATING AGENT-BASED REGIMENS

The German Low-Grade Lymphoma Study Group (GLSG) data published in 2009 underscored the value of concurrently using rituximab with conventional chemotherapy and put R-CHOP as one of the viable alternatives for the treatment of WM in medically fit patients.[7] The GLSG trial was an open-label, phase 3 study involving treatment naïve patients with advanced-stage indolent lymphomas (follicular lymphoma, LPL and mantle cell lymphoma). Buske and colleagues reported on the subset analysis of patients with active WM (n = 48 of 64 evaluable patients with LPL) who were randomly assigned in the GLSG study to receive CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone; n = 25) or rituximab plus CHOP (n = 23) for 4 to 8 3-week cycles. The median age of patients at study entry was 61 (range 37–78) years. Although the complete remission (CR) rates were disappointingly low and similar between the 2 regimens (9% vs 4%; $P = .60$), a considerably higher ORR was observed with R-CHOP (91%) compared with CHOP alone (60%; $P = .019$) which translated into a substantially longer time-to-treatment failure (TTF, the primary endpoint of the study) with R-CHOP (median 63 months) compared to with the CHOP arm (median 22 months, $P = .024$).[7] Alopecia, mucositis, infections, nausea, and vomiting comprised the main nonhematological toxicities, occurring at similar frequencies with both regimens, though the sample size was small to detect differences.[7]

A subsequent single-arm phase 2 Eastern Cooperative Oncology Group (ECOG) trial, E1A02, confirmed the high degree of ORR achieved with the R-CHOP regimen (100%), with a major response rate (MRR) of 91%, and at the short median follow-up of approximately 18 months. The median duration of response (DOR) was not reached.[8] This study was activated in 2004 after the GLSG trial had completed its accrual but was prematurely closed due to poor enrollment (n = 16), highlighting the need for international collaboration, with close involvement of advocacy groups for successfully bringing the trials involving a rare malignancy such as WM to fruition.

Patients with WM are inherently predisposed to peripheral neuropathy. Although there were no major differences encountered in the treatment-emergent toxicities between the 2 regimens in the GLSG substudy, myelosuppression, predominantly neutropenia, and vincristine-induced neurotoxicity (encountered in nearly 50% of the patients despite omission of the drug in the subsequent cycles at first signs of neuropathy) make the CHOP-based regimens unappealing, particularly for the frail or less medically fit patients with WM.[9] On the other hand, the dexamethasone, rituximab, and cyclophosphamide (DRC) regimen, first introduced by the Greek Group, retained the steroid (dexamethasone, instead of prednisone), CD20-directed therapy (rituximab) and the alkylator (cyclophosphamide given orally), but eliminated the vinca alkaloid (vincristine) and the anthracycline (doxorubicin), thereby making it more appealing

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than R-CHOP for the less-fit patient population. In a single-arm phase 2 trial, 72 patients with previously untreated WM were given the DRC regimen.[10,11] This study reported an ORR of 83%, with 67% of these patients achieving a partial response (PR) and 7% achieving a CR. The median progression-free survival (PFS) was 35 months (vs 23 months with rituximab single-agent), the median time-to-next treatment was 51 months and the median overall survival (OS) was 95 months (8-year OS rate of 47%).[10] Notably, approximately 3% of patients developed myelodysplastic syndrome (MDS) during a median follow-up period of 8 years (range 7–10 years), and ~10% transformed to diffuse large B-cell lymphoma (DLBCL). The regimen was well tolerated, particularly with low rates of neutropenia and thrombocytopenia. It has, however, not been prospectively compared with R-CHOP (no longer commonly used outside of histologic transformation to DLBCL) or BR.

Soon after the promising results of the DRC study were initially reported, the Mayo Clinic Group examined the incremental value of incorporating lenalidomide (20 mg PO, days 1–21) into the modified DRC backbone in a single-arm phase 2 trial for indolent lymphomas. Among the evaluable patients with WM, the ORR was 80%, (7% CR and 73% PR). The median PFS for the cohort of patients with WM was 38 months and the median OS had not been reached. While in this trial, lenalidomide could be safely combined with DRC, the results did not show an advantage of using it concurrently.[12] More recently, the results of ECWM-1 trial that again built upon the DRC backbone were published. The ECWM-1 (NCT01788020) study, a randomized-controlled phase 3 clinical trial involving patients with previously untreated WM, assessed the effect of adding bortezomib, a first-generation proteasome inhibitor with established activity in WM, to a modified DRC regimen, administered once every 4 weeks with subcutaneous rituximab, following the first intravenous dose. Therefore, in this trial, with PFS as the primary endpoint, a quadruplet, B-DRC was compared with a control arm of a modified DRC regimen. The investigators indicated that the increasing use of ibrutinib, a BTKi, substantially slowed the accrual rate, leading to the trial's premature closure. Overall, 204 patients were enrolled in the study for which the ORR at the end of treatment (six cycles) appeared comparable between the 2 groups: 95% for B-DRC versus 87% for DRC, $P = .07$; however, at the end of the 3 cycles, ORR and major responses were observed in a higher proportion of patients who were treated with B-DRC [ORR 79 versus 57%, and major response rate 65% versus 33%, $P < .01$]. Ultimately, as the best response, the MRR of 85% and 82% were attained with B-DRC and DRC, respectively, $P = .60$. A numerically higher proportion of patients who were treated with B-DRC achieved a deeper response (very good partial response [VGPR] or better rates 33% vs 21%). The responses were attained faster in patients on B-DRC (median time-to-first response for B-DRC was 3.0 vs 5.5 months for DRC]) Importantly, no difference in the 2-year PFS rates was noted between the 2 arms (81% with B-DRC vs 73% with DRC $P = .32$). The PFS rate was similar to the 2-year PFS rate of 67% achieved with the classic DRC regimen, and the rates of peripheral neuropathy, as expected, were higher with B-DRC (18% vs 3%).[13,14] Although the addition of bortezomib to DRC could hasten the attainment of deeper remission among patients in need of a rapid response, these data primarily confirmed that DRC remains an attractive triplet for patients with WM, with a more acceptable toxicity profile, and minimal lymphopenia (3%–5% vs >50% with BR) a factor that may play a role in selecting bridging therapy options in the era of chimeric antigen receptor (CAR) T-cells-based approaches that are being evaluated in patients with relapsed and/or refractory WM.[15]

Bendamustine exhibits the characteristics of an alkylating agent and a purine nucleoside with a favorable toxicity profile. Bendamustine-rituximab (BR) became one of

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the widely adopted frontline CIT regimens for WM following the results of the StiLNHL1-2003 trial, a landmark phase 3 randomized controlled, noninferiority study that compared bendamustine and rituximab versus R-CHOP in 447 patients with mantle-cell lymphoma and indolent lymphomas, including a subset of 41 patients with LPL/WM.[16] The subset analysis reported a longer PFS with BR (69.5 months compared with 28.1 months; hazard ratio [HR] 0.33, $P = .003$) with R-CHOP, despite equally high ORR in both arms (96% with BR and 94% with R-CHOP) among patients with previously untreated WM. Neither regimen was successful in inducing CRs, and OS rates were similar at the time of the last report, although the sub-performance of the control (R-CHOP) arm in this study with respect to the PFS endpoint compared with the R-CHOP arm of the GLSG trial was noteworthy.[7] Along with the StiLNHL1-2003 trial data, the BRIGHT trial comparing BR versus R-CHOP/R-CVP in indolent lymphomas confirmed the superiority of BR on PFS (5-year PFS rate of 65% vs 56%, HR 0.6, $P = .002$). Only 11 out of the 447 patients had a diagnosis of LPL/WM in this study.[17,18] However, it was the subsequent larger, StiLNHL7-2008 trial involving 296 patients that reaffirmed the remarkable efficacy of BR induction, although its primary objective was to assess the role of rituximab maintenance among the newly diagnosed patients with active WM who had achieved at least a PR to 6 cycles of BR plus 2 additional cycles of rituximab.[16,19] The median PFS with BR induction alone was 69 months, almost identical to the findings of the preceding StiLNHL1-2003 trial (median PFS 69.5 months, **Table 1**).[16,19] Only 7 cases of second myeloid malignancies were noted in both BR and R-CHOP groups among 447 patients despite a long median follow-up of almost 10 years.[20] The patients in the maintenance arm received rituximab every 2 months for 2 years.[20] Among patients achieving at least a PR to BR, the median PFS was 101 months in the rituximab maintenance cohort versus 83 months in the BR alone cohort, but this difference in outcome was not statistically significant (HR 0.80; $P = .32$). The study results have not been published yet but the most recent update in 2022 demonstrated the median PFS of 118 months with maintenance compared with 106 months patients in the rituximab maintenance arm following BR induction, $P = .27$, after 118 months of follow-up.[16,21] The OS rates were also similar, contradicting the data from retrospective studies suggesting the benefit of using rituximab maintenance therapy among the responders.[22,23] However, a subset of patients above the age of 65 showed significantly longer PFS with maintenance in an unplanned posthoc analysis of the StiLNHL7-2008 trial, suggesting there might be a benefit of maintenance therapy in elderly patients. This issue can only be settled with prospective studies in specific subsets of patients. Additionally, the StiLNHL7-2008 demonstrated that the progression within 24 months of initiation of BR portended dismal survival, underscoring the need to develop novel targeted therapies for this subset of patients.[24]

A major adverse effect of BR is myelosuppression, in addition to lymphodepletion. In the StiLNHL1-2003 and BRIGHT trials, respectively, grade 3/4 lymphopenia was reported in 62% to 74% of patients treated with BR as compared with 30% to 43% of patients in the control arm.[16,17] Importantly, alopecia is not observed with BR (0% in the StiLNHL1 trial), and the rates of paresthesias are markedly lower than R-CHOP. However, cutaneous adverse events, such as erythema (16% vs 9%) and allergic skin reaction (15% vs 6%) were higher with BR than R-CHOP.[16] Second myeloid malignancies are an important concern when treating patients with CIT. In the most recent update of the StiL trial, after 86 months of follow-up, 1 of 296 patients treated with BR developed myelodysplastic syndrome and none had acute leukemia.[21] Another retrospective study, with a 9-year median follow-up, reported 0.5% per-person per-year of developing MDS or AML which translated to a cumulative incidence of 6% after treatment

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Table 1
Results from clinical trials with chemoimmunotherapy as frontline treatment in Waldenström macroglobulinemia

Regimen	Study	Phase	N (TN)	ORR (%)	MRR %,	CR%/ VGPR%	PFS (m)[a]	OS (m)[a]	Comments
Dexamethasone/ Rituximab/ Cyclophosphamide (DRC)[10,11,14]	Kastritis et al,[10] 2015	II	72	83	74	7	35	95	A well-tolerated, 21-d moderately effective regimen.
	Buske et al,[1] 2021	II	96	91	82	1/20	73% at 2 y	Not reached at 2 y	Six 28-d cycles of DRC regimen using SQ rituximab from C2-C6 shows similar 2-y PFS to the 6 courses of the original 21-d C.
Rituximab/ Bendamustine (BR)[16,24]	StiLNHL1-2003	III (subgroup analysis of WM cohort)	41	96		0	69.5		Although PFS of BR was markedly higher than that of R-CHOP (control arm, median 28 m), no OS difference was noted at 45m of follow up
	StiL NHL7-2008 MAINTAIN trial	III	266	93	88	1/24	69	NR	Adding rituximab maintenance post-BR (x 6C)+ R (x 2C) among pts with ≥PR did not statistically improve PFS or OS.
Bortezomib/Dex/ Rituximab/ Cyclophosphamide (B-DRC)[14]	Buske et al,[7] 2009	II	96	95	85	5/27	81% at 2 y	Not reached at 2y	Adding bortezomib to DRC showed no net PFS benefit against the DRC control. B-DRC increased the risk of neurotoxicity, but the time to deeper responses was shorter.
Lenalidomide/ Rituximab/ Cyclophosphamide/ Dex (L-RCD)[12]	Rosenthal et al,[12] 2017	II	15	80	80	7	38	Not reached at 23 mo	Grade ≥3 neutropenia was observed in 42% of patients.

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Fludarabine/ Rituximab (FR)[47]	Treon et al,[36] 2011	II	27	96	89	5[d]/33	78[b]	Not reported	Pneumocystis carinii pneumonia and second myeloid malignancies, and disease transformation to aggressive lymphoma is a concern.
Rituximab/ Cladribine (R-2CDA)[49]	Laszlo et al,[48] 2010	II	16	94	79	24[d]	Not reached[c]	93% at 43 mo follow-up.	No major infections were observed despite the lack of antimicrobial prophylaxis. No disease transformation was noted at 43 mo follow-up.
Fludarabine/ Cyclophosphamide/ Rituximab (FCR)[50]	Auer et al,[49] 2016 R2W	II	17	82	77	0/18	Not reached at 18 mo	88% at 18m	Grade $\geq$3 hematologic toxicities were higher with FCR compared to BCR
Bortezomib/ Cyclophosphamide/ Rituximab (BCR)[62]	Auer et al,[49] 2016 R2W	II	42	98	79	1/19	Not reached at 18 mo	98% at 18m	No grade 3 or higher neuropathy was reported.
Pentostatin/ Cyclophosphamide $\pm$ Rituximab (PCR)[62,63]	Hensel et al,[61] 2005	II	9	77[d]	62[d]	15[d]	Not reported	Not reported	ORR was higher when R added to PC.
	Herth et al,[62] 2015	II	21	88[d]	68[d]	0/16[d]	84% at 2 y[d]	100% at 2 y[d]	Another small study showing the efficacy and safety of the adenosine deaminase inhibitor, pentostatin, combination therapy.

Results are reported for the treatment naïve subset only for studies that include relapsed/refractory patients in addition to the treatment naïve patients.

Abbreviations: BCR, bortezomib, cyclophosphamide, and dexamethasone; B-DRC, bortezomib, dexamethasone, rituximab, and cyclophosphamide; BR, bendamustine and rituximab; C, cycle; FR, fludarabine and rituximab; m, months; MRR, major response rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; pts, patients; R-2CDA, rituximab, and cladribine, R, rituximab; y, years.

[a] Median unless specified.

[b] Time to progression (TTP).

[c] Time-to-treatment failure (TTF).

[d] For treatment-naïve and relapsed/refractory patients combined.

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with bendamustine in patients with non-Hodgkin lymphoma.[25] Following the release of the StiLNHL1-2003 trial results, the remarkable efficacy and the relatively manageable toxicity profile of the BR doublet have been confirmed by other groups.[26–29]

In the French Innovative Leukemia Organization (FILO) multicenter, retrospective study involving 69 patients between 45 and 88 years of age (median 69 years), all patients except one achieved minor response or better, leading to an ORR of 97% with BR; the major response rate was 96%, with 19% attaining CR and 56% achieving VGPR or better.[29] The responses continued to deepen over 18 months, with cumulative ORR rates improving from 70% at 3 months, 91% at 6 months, to 97% at 18 months.[29] Thirty (44%) patients required either a dose reduction of bendamustine or a shorter course of BR, that is, fewer than 6 cycles. In the most recent update of this study, after a median follow-up of 68.5 months, the median OS was not reached, and the median PFS was 82 months (range: 75-NR). The 2-year rates of PFS and OS were remarkably high at 87% and 97%, respectively. Patients who received an abbreviated course had comparable PFS rates, consistent with the findings of a few other retrospective studies suggesting equivalent outcomes with 4 versus 6 cycles of BR. However, the UK group recently demonstrated inferior PFS in patients who received a lower cumulative dose of bendamustine during induction suggesting that 4 cycles might be insufficient.[30] In the FILO study, neither the presence of *MYD88*^{mut} nor *CXCR4*^{mut} impacted the response to BR. About one-half of the patients had prolonged cytopenias and 2 patients had treatment-related myeloid neoplasms.[28,29]

In a recent international collaborative effort, 208 patients who had received BR induction without rituximab maintenance were analyzed. After a median follow-up of 4 years, the estimated median PFS was approximately 70 months, mirroring the data generated by the STiL trials. The small subcohort of patients (11%) who had progression of disease (POD) within 24 months of BR therapy demonstrated shorter OS (5-year OS rate, 75% vs 94% for the rest, $P = .03$). This study also confirmed that BR was active irrespective of the *MYD88* mutation status (4-year PFS rate was 71%). Among the small subset of patients (n = 48; 23%) in whom *CXCR4* mutation status was available, 28% exhibited *CXCR4* mutation, with a trend toward shorter PFS (median PFS 3.9 years vs 5.5 years for the subgroup with *CXCR4*^{WT} genotype, $P = .056$), hinting at the possibility of *CXCR4* mutations adversely affecting the outcome of patients on CIT as well, similar to the observations made with BTKi-based therapies.[31]

A Mayo Clinic study comparing BR (n = 83) to DRC (n = 92) and BDR (n = 45) demonstrated superior ORR with BR (98% vs 78% with DRC and 84% with BDR; $P = .003$) in the frontline setting. The median PFS was also superior with BR (median 5.2 years with BR vs 4.3 for DRC vs 1.8 years for BDR; $P < .001$), though no difference in the OS was observed among the 3 cohorts. Notably, the PFS with BDR was significantly shorter than the previously published reports in clinical trials with this regimen. Notably, the response rates for BR, DRC, or BDR regimens were not affected by the *MYD88* mutation status, but the study did not address the impact of *CXCR4* mutation on the different CITs.[32] The superiority of BR compared with other CIT regimens has also been demonstrated in a retrospective study by the DFCI Group and the *WhiMSICAL, a global patient-derived data registry for WM*.[33,34]

An important retrospective, multicenter international collaborative study compared the outcomes of patients with treatment-naïve WM who were administered either BR or ibrutinib as primary therapy. The study excluded patients who received rituximab maintenance therapy and those with the *MYD88*^{WT} genotype. In this analysis of age-matched patients, after a median follow-up of 4.2 years, the PFS rates were similar among the 2 treatment groups; 4-year PFS was 72% and 78% with BR and ibrutinib, respectively, $P = .14$. There was no OS difference between the 2 cohorts.

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However, despite similar PFS and OS, the CR rates were substantially higher with BR (20% as compared with 2%, p=<0.001) as were the rates of VGPR or deeper response (50 vs 33% $P = .009$).[33] The WhiMSICAL global registry reported substantially longer time-to-next therapy with BR (n = 74) compared with BTK inhibitors (n = 23) in the frontline setting. Still, the baseline characteristics, including patient genotype, were unavailable in this analysis that was reliant on patient-reported rather than formally documented data.[35]

Another retrospective multicenter, international collaborative study reported the outcomes of 319 treatment-naive patients who were administered fixed-duration or Bortezomib, Dexamethasone, Rituximab (BDR), or a CIT (either BR or DRC). Importantly, this study identified that the depth of response to fixed-duration treatment was associated with prognosis. In the multivariate analysis, attaining a major response was independently associated with better PFS (HR 0.33, $P < .001$), time-to-next therapy (TTNT; HR 0.23, $P < .001$), and OS; (HR 0.31; $P = .001$) compared with patients who achieved less than a major response at the 6-month landmark from the commencement of fixed-duration treatment.[26]

The scant data with BR that are available for the relapsed and/or refractory (RR) setting are less impressive than the data in the frontline setting.[33,35,36] In a small phase 2 trial involving 30 patients with RRWM who were initially treated with BR, the median number of prior therapies was 2 (range 1–9), the ORR was 83%, VGPR and PR rates were 17% and 67%, respectively.[27] However, the median estimated time-to-progression (TTP) was 13 months, with protracted myelosuppression among patients previously exposed to purine analogs. One patient previously exposed to fludarabine and rituximab, and cyclophosphamide, prednisone, and rituximab developed MDS.[27] In a larger study of 71 patients with RRWM, after a median of 2 lines of therapy (most patients were exposed to alkylators and rituximab), ORR and major response rate were 80% and 75%, respectively, the CR rates were low at 7%. The quality of response was superior with the 90 mg/m2 dose of bendamustine. No cases of IgM flare were reported and among patients with high IgM levels, the initial infusion was postponed preventing hyperviscosity syndrome. The PFS rates were approximately 60% at 2 years, in contrast with 87% at 2 years in the treatment-naïve population in the FILO study. No patients developed a myeloid malignancy, but the follow-up was only 19 months.[37] These results suggest that maximal benefit, with a long treatment-free interval, is likely associated with using BR as primary rather than salvage therapy.

PURINE-ANALOG BASED REGIMENS

Purine/Nucleoside analogs, fludarabine, and cladribine (2-CDA), have a long track record in WM, with extensive data generated over the years in the frontline and salvage setting. The overall response rates as primary therapies are somewhat higher (40%–90% vs 3%–50% in RR setting).

Purine analogs can incorporate into the DNA and RNA strands and rapidly inhibit DNA replication plus gene transcription, affecting both the dividing and nondividing cells. Often irreversible, the major neurotoxicities (seizures, optic neuritis, cortical blindness, confusion) were not encountered with the lower doses of fludarabine used in lymphoproliferative disorders. In 1990, fludarabine was first used in 10 patients with RR and one with TN WM, with a single patient in the frontline setting and 40% in the relapsed-refractory setting achieving at least a partial response.[38] It has subsequently been studied extensively both as monotherapy as well as in combination with other agents, including alkylators and CD20 monoclonal antibodies, rituximab, and ofatumumab.[39–43]

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It has not been directly compared with the other commonly used purine analog cladribine, but their tolerability and efficacy appear to be comparable.

Although it is only available as an intravenous formulation in the US, in a large, multicentric European phase 3 trial, oral fludarabine was compared with oral chlorambucil as primary therapy in 339 patients with WM (**Table 2**). Superior outcomes, including longer OS, were observed in the fludarabine arm. The study highlighted how the natural history of even an indolent lymphoma such as WM, with a relapsing-remitting course, could be determined by the choice of the initial therapy.[40] However, eventually, the case for its use in the frontline setting remained weak, given the associated toxicities, including prolonged myelosuppression (neutropenia and thrombocytopenia), increased risk of opportunistic infections, stem cell damage potentially adversely affecting stem cell mobilization for autologous transplantation, and the risk of histologic transformation as well as treatment-related myeloid malignancies.

Several combination therapies have also been evaluated; in particular, when combined with cyclophosphamide, a synergistic action has been observed as the cyclophosphamide-induced DNA breaks remain unrepaired in the presence of fludarabine. Tamburini and colleagues examined fludarabine plus cyclophosphamide (FC) involving 49 patients, 35 previously treated. An ORR was noted in 78% of the patients and the median TTF was 27 months. Notably, the responses with fludarabine may be delayed (median time of 10.8 months) and may continue to deepen even after the completion of treatment, similar to the observation made with several non-purine analog-based CIT regimens.[44,45] *In vitro* data also suggested synergistic activity with rituximab. Rituximab enhances cytotoxicity by fludarabine which also reciprocally, through the reduction of CD55 and CD59 expression on lymphocytes, increases their sensitivity to antibody-mediated apoptosis through caspase 3 and caspase 9 activation.[46] Consequently, better quality of responses and more durable responses are observed when fludarabine is combined with immunochemotherapy. In the study by Treon and colleagues, evaluating the fludarabine-rituximab combination in 43 patients of whom 27 (63%) were treatment-naïve, the ORR and MRR were 95%, and 86%, respectively.[47] After a median follow-up of 40.3 months, the median estimated time-to-progression (TTP) for the entire cohort was 51.2 months. It was significantly shorter in patients who received fludarabine and rituximab (FR) in the salvage setting (estimated 38 months) compared with FR as primary therapy (estimated 78 months). In this study, 7% of patients transformed to aggressive lymphoma. In comparison, another 7% of patients had developed AML/MDS at a median time of 21 months and 39 months, respectively, from the initiation of FR.[47]

Tedeschi and colleagues examined 6 cycles of the FCR (fludarabine, cyclophosphamide, and rituximab) regimen in patients with RRWM (n = 57) and TN with WM (n = 25). The ORR was 88%, with an MRR of 64% at treatment discontinuation, which improved to 76% at the best response. The PFS and OS rates were the same at 96% for 3 years. In a multivariate analysis, only the TN status before FCR (median PFS: 79 months for patients with RR, vs not reached; $P = .02$) and age (median PFS 46 months for patients over 65, vs not reached; $P = .006$) significantly impacted PFS.[48] Laszlo and colleagues evaluated subcutaneous cladribine with rituximab in patients with TN and RR. A high ORR of 90% was observed.[49] Clinicians should remain vigilant to additional supportive care, including growth factor support, *Pneumocystis jiroveci,* and herpes prophylaxis that patients may require on purine analog combinations, particularly those who are heavily pretreated.

The NCT01592981 (R2W) trial, is a non-comparative phase 2 study, with a primary endpoint of ORR. The trial randomly assigned 60 treatment-naïve patients in a 2:1 fashion to either subcutaneous bortezomib, oral cyclophosphamide, and intravenous

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Table 2
Results from clinical trials of chemotherapy alone (without immunotherapy) in Waldenström macroglobulinemia

Study	Phase	Treatment	Patients (n)	ORR/MRR (%)	CR (%)	PFS[a] and/or OS
Dimopoulos et al,[38] 1993	II	Fludarabine	2, TN 26, RR	100 (TN), 31 (RR)/36[b]	4	DOR (median): 38 mo[b] OS (median): 32 mo[b]
Leblond et al,[39] 2009	III	Fludarabine vs chlorambucil	339, TN	46 vs 36/ - vs -	-	PFS (median): 37.8 mo vs 27.1 mo OS (median): NR vs 69.8 mo
Foran et al,[40] 1999	II	Fludarabine	19, TN	79/79	5	PFS (median): 3.4 y OS (median): NR
Dhodapkar et al,[41] 2001 S9003.	II	Fludarabine	118, TN 64, RR	38/23	3	5-y PFS: 62% (TN), 36% (RR) 5-y OS: 49% (TN), 30% (RR)
Tamburini et al,[44] 2005	II	FC	14, TN 35, RR	85/-	-	TTF (median)[b]: 27 mo OS (median)[b]: NR
Dimopoulos et al,[63] 2003	II	FC	2, TN 9, RR	55[b]/55[b]	-	PFS (median): 24 mo[b] OS at 2 y: 70%[b]
Kyle et al,[64] 2000	II	Chlorambucil	46, TN	70/-	-	OS (median): 5.4 y

Abbreviations: DOR, duration-of-response; FC, fludarabine and cyclophosphamide; MRR, major response rate; not reported; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RR, relapsed and/or refractory; TN, treatment-naïve; TTF, time-to-treatment failure.

[a] Some studies may have reported DOR or TTF instead of PFS.

[b] Responses for patients with TN and RR combined.

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rituximab (BCR) or FCR for 6 cycles. It showed an ORR of 98% and 79% and MRR of 82% and 77%, respectively, with BCR and FCR.[50] The reduced rates and absence of grade 3 or higher of treatment-emergent peripheral neuropathy in the BCR arm were ascribed to the change in the route (from intravenous to subcutaneous) and frequency (from twice weekly to weekly) of bortezomib administration. After 18 months of follow-up, 3 patients in the BCR arm had progressed but none in the FCR arm (n = 17). However, despite the short follow-up, three deaths were reported: one from pneumonia in the BCR arm and 2 MDS-related in the FCR arm. No cases of MDS were observed in the BCR arm. The final results of this trial are awaited.[50]

Given the associated toxicities and the availability of equally, if not more effective therapies, purine analogs are used only in patients with RR disease when safer, effective alternatives are unavailable.

IMPACT OF UNDERLYING WALDENSTRÖM MACROGLOBULINEMIA-RELATED SOMATIC MUTATIONS ON PATIENT OUTCOMES WITH CHEMOIMMUNOTHERAPY

Studies have identified that *MYD88*^{WT} WM is associated with a higher risk of histologic transformation to an aggressive lymphoma and the progression of smoldering WM to active disease.[51,52] Unlike the observation made with ibrutinib, the first-generation BTKi, within the sparsely available data, the patients' *MYD88* genotype does not impact CIT-treated patients' outcomes. Compared with *CXCR4*^{WT}, a concurrent alteration in *CXCR4* with *MYD88*^{mut} confers an inferior response to BTKi-based therapy but its impact on the response to CIT is not well studied. *CXCR4*$^{WHIM/NS}$ mutations in smoldering WM may also be associated with a shorter treatment initiation time but do not appear to impact OS so far.[53,54] A recent multi-institutional collaborative effort, however, showed a trend toward inferior response and shorter PFS in patients that harbored *CXCR4* mutations compared with those that exhibited *CXCR4*^{WT} genotype on BR primary therapy.[31] The mutational data for *MYD88* and *CXCR4* genes have helped pave the way for personalized treatment for WM, especially about ibrutinib monotherapy. Still, their impact on outcomes with conventional CIT remains to be fully elucidated. Additionally, generally a marker of poor prognosis, how the varying proportions of *TP53* alterations reported in WM by the recent next-generation sequencing-based studies impact the outcome of patients treated with CIT is not yet well studied.[55–58]

The Case for Chemoimmunotherapy Use in the Frontline Setting

Despite the emergence of multiple effective treatments in the frontline setting for patients with WM, only some randomized trials have established the superiority of one regimen over the other. Various factors impact the decision-making for optimal frontline therapy, including the mutational profile, patient preference, performance status, and comorbidities.

In patients with TN symptomatic WM, we administer 6 cycles of BR without maintenance rituximab. This approach is effective even with *MYD88*^{WT,} for which BTK inhibitors, particularly ibrutinib, have shown substantially reduced efficacy. Furthermore, among the BTK inhibitor-naïve patients, the efficacy of BTKi-based salvage regimens appears to remain uncompromised.

A fixed duration of treatment, achievement of deep and durable responses (median PFS of 5.5–6 years in all patients and nearly 9 years for patients who achieve at least a partial remission), along with the short-lived adverse effects that are manageable and predominantly confined to the 6-month duration of therapy are the major reasons for adopting BR as the primary regimen for WM. However, one should remain vigilant regarding the development of myeloid malignancies, prolonged lymphodepletion,

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and immunosuppression. In contrast to the incidence of the second myeloid malignancies (0.5% per person per year) with fixed-duration BR as salvage treatment, MDS and AML were exceedingly uncommon when BR was used as primary therapy for indolent lymphomas.[25,59] In patients with a serum IgM level of more than 4000 mg/dL, rituximab may be omitted from the initial couple of cycles of CIT to avoid an IgM flare that could worsen the symptoms of hyperviscosity, cryoglobulinemia or neuropathy.[60] In elderly patients above 70 years of age, we reduce the standard recommended dose of bendamustine from 90 mg/m^2 on days 1 and 2, to 70 mg/m^2/d over 2 days. For frail patients, DRC for six cycles is a viable alternative. While formal analyses have not been performed, limited duration BR is likely more cost-effective than continuous BTKi therapy.

Ongoing Studies with Chemoimmunotherapy as Primary Treatment

An ongoing single-arm, phase 2 Canadian study (NCT04624906, BRAWM) is assessing the efficacy of bendamustine and rituximab for six 28-day cycles concomitantly with the second-generation BTKi, acalabrutinib for an abbreviated duration of 1 year in previously untreated patients with WM. However, the primary study outcome measure is the rate of VGPR or deeper remission as the best response, the value of which as a surrogate for PFS and OS is unclear.

Another ongoing study (NCT05099471, VIVA-1), developed for previously untreated patients on the heels of the promising activity and tolerability of venetoclax monotherapy demonstrated among patients with RRWM,[61] is a phase 2, open-label, randomized trial designed to explore whether fixed-duration venetoclax plus rituximab combination increases the rate of CR/VGPR 12 months after randomization compared with DRC, irrespective of the patient genotype.

In summary, CIT is a highly effective approach for patients with WM. High-level evidence suggests that the choice of the initial regimen can potentially change the natural history of WM, a malignancy that remains incurable. True advances in the field would be made when substantial improvement over the high bar set by the BR therapy is overcome by other limited-duration regimens in the frontline setting, with minimal acute and long-term toxicities.

CLINICS CARE POINTS

- A phase 3 randomized controlled trial has shown higher efficacy and a more favorable toxicity profile of the bendamustine-rituximab (BR) compared with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) among patients with treatment-naïve WM.
- High level evidence comparing BR and DRC regimens is absent.
- DRC appears to be inferior to BR in cross-trial comparisons and retrospective series involving treatment-naïve patients with WM.
- Purine analog-based CIT has been extensively evaluated in WM, although its use has waned, even in the multiply relapsed patient population, as effective and safer alternatives have emerged.

CONFLICT OF INTEREST

P. Kapoor is the principal investigator of trials for which Mayo Clinic has received research funding from Amgen, United States, Regeneron, United States, Bristol Myers

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Squibb, United States, Loxo Pharmaceuticals, Ichnos, Karyopharm, Sanofi, United States, AbbVie and GlaxoSmithKline. P. Kapoor has served on the Advisory Boards of BeiGene, Pharmacyclics, X4 Pharmaceuticals, Kite, Oncopeptides, Angitia Bio, GlaxoSmithKline, AbbVie, and Sanofi. J. Paludo reports Honoraria to institution: Abbvie and research funding to institution: Karyopharm and Biofourmis. J. Abeykoon reports research funding from Qurient therapeutics.

REFERENCES

1. Buske C, Leblond V. Waldenstrom's macroglobulinemia. In: Dreyling M, Ladetto M, editors. Indolent lymphomas. New York: Springer; 2021. p. 143–61.
2. Sekhar J, et al. Waldenstrom macroglobulinemia: a Surveillance, Epidemiology, and End Results database review from 1988 to 2005. Leuk Lymphoma 2012; 53(8):1625–6.
3. Fonseca R, Hayman S. Waldenström macroglobulinaemia. Br J Haematol 2007; 138(6):700–20.
4. Morel P, Merlini G. Risk stratification in Waldenström macroglobulinemia. Expert Rev Hematol 2012;5(2):187–99.
5. Dimopoulos MA, et al. Predictive factors for response to rituximab in Waldenstrom's macroglobulinemia. Clin Lymphoma 2005;5(4):270–2.
6. Furman RR, et al. Once-weekly ofatumumab in untreated or relapsed Waldenström's macroglobulinaemia: an open-label, single-arm, phase 2 study. Lancet Haematol 2017;4(1):e24–34.
7. Buske C, 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): 153–61.
8. Abonour R, et al. Phase II Pilot Study of Rituximab + CHOP in Patients with Newly Diagnosed Waldenström's Macroglobulinemia, an Eastren Cooperative Oncology Group Trial (Study E1A02). Blood 2007;110(11):3616.
9. Okada N, et al. Risk Factors for Early-Onset Peripheral Neuropathy Caused by Vincristine in Patients With a First Administration of R-CHOP or R-CHOP-Like Chemotherapy. J Clin Med Res 2014;6(4):252–60.
10. Kastritis E, et al. Dexamethasone, rituximab, and cyclophosphamide as primary treatment of Waldenström macroglobulinemia: final analysis of a phase 2 study. Blood 2015;126(11):1392–4.
11. Dimopoulos MA, et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. J Clin Oncol 2007;25(22): 3344–9.
12. Rosenthal A, et al. A phase 2 study of lenalidomide, rituximab, cyclophosphamide, and dexamethasone (LR-CD) for untreated low-grade non-Hodgkin lymphoma requiring therapy. Am J Hematol 2017;92(5):467–72.
13. Buske C, et al. Bortezomib in Combination with Dexamethasone, Rituximab and Cyclophosphamide (B-DRC) As First - Line Treatment of Waldenstrom's Macroglobulinemia: Results of a Prospectively Randomized Multicenter European Phase II Trial. Blood 2020;136(Supplement 1):26.
14. Buske C, et al. Bortezomib-Dexamethasone, Rituximab, and Cyclophosphamide as First-Line Treatment for Waldenström's Macroglobulinemia: A Prospectively Randomized Trial of the European Consortium for Waldenström's Macroglobulinemia. J Clin Oncol 2023;22:01805.

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15. Saito H, et al. Prolonged lymphocytopenia after bendamustine therapy in patients with relapsed or refractory indolent B-cell and mantle cell lymphoma. Blood Cancer J 2015;5(10):e362.
16. Rummel MJ, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet (London, England) 2013;381(9873):1203–10.
17. Flinn IW, et al. First-Line Treatment of Patients With Indolent Non-Hodgkin Lymphoma or Mantle-Cell Lymphoma With Bendamustine Plus Rituximab Versus R-CHOP or R-CVP: Results of the BRIGHT 5-Year Follow-Up Study. J Clin Oncol 2019;37(12):984–91.
18. Flinn IW, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood 2014; 123(19):2944–52.
19. Rummel MJ, et al. Bendamustine Plus Rituximab Followed By Rituximab Maintenance for Patients with Untreated Advanced Follicular Lymphomas. Results from the StiL NHL 7-2008 Trial (MAINTAIN trial) (ClinicalTrials.gov Identifier: NCT00877214). Blood 2014;124(21):3052.
20. Rummel MJ, et al. Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent lymphomas: Nine-year updated results from the StiL NHL1 study. J Clin Oncol 2017;35(15_suppl):7501.
21. Rummel M. Bendamustine plus rituximab followed by rituximab maintenance for patients with untreated advanced follicular lymphomas. Results from the StiL NHL 7-2008 trial (MAINTAIN trial) (ClinicalTrials.gov identifier: NCT00877214). Madrid, Spain: IWWM-11 meeting; 2022.
22. Castillo JJ, et al. Response and survival for primary therapy combination regimens and maintenance rituximab in Waldenström macroglobulinaemia. Br J Haematol 2018;181(1):77–85.
23. Zanwar S, et al. Rituximab-based maintenance therapy in Waldenström macroglobulinemia: A case control study. J Clin Oncol 2019;37(15_suppl):7559.
24. Rummel MJ, et al. Two Years Rituximab Maintenance Vs. Observation after First Line Treatment with Bendamustine Plus Rituximab (B-R) in Patients with Waldenström's Macroglobulinemia (MW): Results of a Prospective, Randomized, Multicenter Phase 3 Study (the StiL NHL7-2008 MAINTAIN trial). Blood 2019; 134(Supplement_1):343.
25. Martin P, et al. Long-term outcomes, secondary malignancies and stem cell collection following bendamustine in patients with previously treated non-Hodgkin lymphoma. Br J Haematol 2017;178(2):250–6.
26. Paludo J, et al. Bendamustine and rituximab (BR) versus dexamethasone, rituximab, and cyclophosphamide (DRC) in patients with Waldenström macroglobulinemia. Ann Hematol 2018;97(8):1417–25.
27. Tedeschi A, et al. Bendamustine and rituximab combination is safe and effective as salvage regimen in Waldenström macroglobulinemia. Leuk Lymphoma 2015; 56(9):2637–42.
28. Laribi K, et al. Bendamustine plus rituximab in newly-diagnosed Waldenström macroglobulinaemia patients. A study on behalf of the French Innovative Leukaemia Organization (FILO). Br J Haematol 2019;186(1):146–9.
29. Laribi K, et al. Long-Term Follow-up of Bendamustine Plus Rituximab Regimen in 69 Treatment Naïve (TN) Patients with Waldenström Macroglobulinemia, a Study on Behalf of the French Innovative Leukemia Organization (FILO). Blood 2022; 140(Supplement 1):3627–8.

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30. Arulogun SO, et al. Bendamustine Plus Rituximab for the Treatment of Waldenström Macroglobulinaemia: Patient Outcomes and Impact of Bendamustine Dosing. Blood 2020;136:10–1.
31. Zanwar S, et al. P1159: a multicenter, international collaborative study evaluating frontline therapy with bendamustine rituximab for Waldenström macroglobulinemia. HemaSphere 2022;6.
32. Abeykoon JP, et al. Assessment of fixed-duration therapies for treatment-naïve Waldenström macroglobulinemia. Am J Hematol 2021;96(8):945–53.
33. Tohidi-Esfahani I, et al. WhiMSICAL: A global Waldenström's Macroglobulinemia patient-derived data registry capturing treatment and quality of life outcomes. Am J Hematol 2021;96(6):E218–22.
34. Abeykoon JP, et al. Bendamustine rituximab (BR) versus ibrutinib (Ibr) as primary therapy for Waldenström macroglobulinemia (WM): An international collaborative study. J Clin Oncol 2022;40(16_suppl):7566.
35. Perera ND, et al. Prognostic impact of depth of response in Waldenström macroglobulinemia patients treated with fixed duration chemoimmunotherapy. J Clin Oncol 2021;39(15_suppl):8049.
36. Treon SP, et al. Bendamustine therapy in patients with relapsed or refractory Waldenström's macroglobulinemia. Clin Lymphoma Myeloma Leuk 2011;11(1):133–5.
37. Kantarjian HM, et al. Fludarabine therapy in macroglobulinemic lymphoma. Blood 1990;75(10):1928–31.
38. Dimopoulos MA, et al. Fludarabine therapy in Waldenström's macroglobulinemia. Am J Med 1993;95(1):49–52.
39. Leblond V, et al. Results of a randomized trial of chlorambucil versus fludarabine for patients with untreated Waldenström macroglobulinemia, marginal zone lymphoma, or lymphoplasmacytic lymphoma. J Clin Oncol 2013;31(3):301–7.
40. Foran JM, et al. Multicenter phase II study of fludarabine phosphate for patients with newly diagnosed lymphoplasmacytoid lymphoma, Waldenström's macroglobulinemia, and mantle-cell lymphoma. J Clin Oncol 1999;17(2):546–53.
41. Dhodapkar MV, et al. Prognostic factors and response to fludarabine therapy in patients with Waldenstrom macroglobulinemia: results of United States intergroup trial (Southwest Oncology Group S9003). Blood 2001;98(1):41–8.
42. Thalhammer-Scherrer R, et al. Fludarabine therapy in Waldenström's macroglobulinemia. Ann Hematol 2000;79(10):556–9.
43. Castillo JJ, et al. Deepening of response after completing rituximab-containing therapy in patients with Waldenstrom macroglobulinemia. Am J Hematol 2020;95(4):372–8.
44. Tamburini J, et al. Fludarabine plus cyclophosphamide in Waldenström's macroglobulinemia: results in 49 patients. Leukemia 2005;19(10):1831–4.
45. Furlan A, et al. Low-dose fludarabine increases rituximab cytotoxicity in B-CLL cells by triggering caspases activation in vitro. Leuk Lymphoma 2010;51(1):107–13.
46. Treon SP, et al. Long-term outcomes to fludarabine and rituximab in Waldenström macroglobulinemia. Blood 2009;113(16):3673–8.
47. Tedeschi A, et al. Fludarabine plus cyclophosphamide and rituximab in Waldenstrom macroglobulinemia: an effective but myelosuppressive regimen to be offered to patients with advanced disease. Cancer 2012;118(2):434–43.
48. Laszlo D, et al. Rituximab and subcutaneous 2-chloro-2'-deoxyadenosine combination treatment for patients with Waldenstrom macroglobulinemia: clinical and biologic results of a phase II multicenter study. J Clin Oncol 2010;28(13):2233–8.

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49. Auer RL, et al. R2W: Subcutaneous Bortezomib, Cyclophosphamide and Rituximab (BCR) Versus Fludarabine, Cyclophosphamide and Rituximab (FCR) for Initial Therapy of WaldenstrőM's Macroglobulinemia: A Randomised Phase II Study. Blood 2016;128(22):618.
50. Abeykoon JP, et al. MYD88 mutation status does not impact overall survival in Waldenstrom macroglobulinemia. Am J Hematol 2018;93(2):187–94.
51. Zanwar S, et al. Impact of MYD88(L265P) mutation status on histological transformation of Waldenström Macroglobulinemia. Am J Hematol 2020;95(3):274–81.
52. Varettoni M, et al. Pattern of somatic mutations in patients with Waldenström macroglobulinemia or IgM monoclonal gammopathy of undetermined significance. Haematologica 2017;102(12):2077–85.
53. Poulain S, et al. Genomic Landscape of CXCR4 Mutations in Waldenstrom Macroglobulinemia. Clin Cancer Res 2016;22(6):1480–8.
54. Wang Y, et al. Molecular and genetic biomarkers implemented from next-generation sequencing provide treatment insights in clinical practice for Waldenström macroglobulinemia. Neoplasia 2021;23(4):361–74.
55. Christian A, et al. Importance of sequential analysis of TP53 variation in patients with Waldenström Macroglobulinaemia. Br J Haematol 2019;186(4):e73–6.
56. Gustine JN, et al. TP53 mutations are associated with mutated MYD88 and CXCR4, and confer an adverse outcome in Waldenström macroglobulinaemia. Br J Haematol 2019;184(2):242–5.
57. Poulain S, et al. TP53 Mutation and Its Prognostic Significance in Waldenstrom's Macroglobulinemia. Clin Cancer Res 2017;23(20):6325–35.
58. Penne M, et al. Extended Follow-up of Patients Treated With Bendamustine for Lymphoid Malignancies. Clin Lymphoma, Myeloma & Leukemia 2017;17(10):637–44.
59. Ghobrial IM, et al. Initial immunoglobulin M 'flare' after rituximab therapy in patients diagnosed with Waldenstrom macroglobulinemia: an Eastern Cooperative Oncology Group Study. Cancer 2004;101(11):2593–8.
60. Castillo JJ, et al. Venetoclax in Previously Treated Waldenström Macroglobulinemia. J Clin Oncol 2022;40(1):63–71.
61. Hensel M, et al. Pentostatin/Cyclophosphamide with or Without Rituximab: An Effective Regimen for Patients with Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Clinical Lymphoma and Myeloma 2005;6(2):131–5.
62. Herth I, et al. Pentostatin, cyclophosphamide and rituximab is a safe and effective treatment in patients with Waldenström's macroglobulinemia. Leuk Lymphoma 2015;56(1):97–102.
63. Dimopoulos MA, et al. Treatment of Waldenstrom's macroglobulinemia with the combination of fludarabine and cyclophosphamide. Leuk Lymphoma 2003;44(6):993–6.
64. Kyle RA, et al. Waldenström's macroglobulinaemia: a prospective study comparing daily with intermittent oral chlorambucil. Br J Haematol 2000;108(4):737–42.

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