AHFS Final Determination of Medical Acceptance:
Off-label Use of Rituximab in Combination with Bendamustine for Previously Untreated Indolent Non-Hodgkin's Lymphoma or Mantle Cell Lymphoma

Drug/Drug Combination: Rituximab in combination with bendamustine

Off-label Use: Previously untreated indolent non-Hodgkin's lymphoma (NHL) or mantle cell lymphoma

Criteria Used in Selection of Off-label Use for Review:

- Periodic review of prior Final Determination for the purpose of updating medical acceptance. The current Final Determination supersedes the past determination originally published in October 2008. In 2008, indolent non-Hodgkin's lymphoma and mantle cell lymphoma were addressed separately; however, the current review combined both indications into one determination. At the time of the original review, the use of rituximab in combination with bendamustine for previously untreated indolent non-Hodgkin's lymphoma or mantle cell lymphoma was not fully established.

Strength of Evidence: Level 2 (Moderate strength/quality)

Strength of Study End Point(s): Progression-free survival

Grade of Recommendation: Reasonable choice (Accepted, with possible conditions)

Narrative Summary:

Previously Untreated, Indolent Non-Hodgkin's Lymphoma or Mantle Cell Lymphoma:

Efficacy and safety of bendamustine in combination with rituximab† for the treatment of previously untreated† advanced-stage indolent NHL or previously untreated advanced-stage mantle cell lymphoma† have been studied in two phase 3 studies (Study Group Indolent Lymphomas [StiL] NHL 1-2003 study and BRIGHT).[10001, 10018]

The first study (StiL NHL 1-2003) was a phase 3, open-label, randomized, noninferiority study in which 514 patients received up to 6 cycles of therapy with either bendamustine in combination with rituximab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[10001] Patients with previously untreated mantle cell lymphoma or indolent NHL, including the CD20-positive histologic subtypes follicular lymphoma (grade 1 or 2), Waldenstrom macroglobulinemia, small lymphocytic lymphoma, and marginal-zone lymphoma, were eligible for enrollment in the study.[10001] Patients receiving the bendamustine-rituximab regimen received rituximab 375 mg/m^2 IV on day 1 and bendamustine hydrochloride 90 mg/m^2 IV daily on days 1 and 2 of each 28-day cycle.[10001] Those receiving R-CHOP received rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, doxorubicin hydrochloride 50 mg/m^2 IV, and vincristine sulfate 1.4 mg/m^2 (up to 2 mg) IV on day 1, followed by prednisone 100 mg orally daily on days 1–5 of each 21-day cycle.[10001] The median patient age was about 64 years (range: 31–83); about 78% of patients had stage IV disease, 19% had stage III disease, 54% had follicular lymphoma, and 18% had mantle cell lymphoma.[10001] The primary measure of efficacy was progression-free survival.[10001] Tumor responses were assessed using the World Health Organization (WHO) criteria.[10001]

At a median follow-up of 45 months, bendamustine in combination with rituximab was noninferior to R-CHOP in terms of progression-free survival; median progression-free survival was 69.5 and 31.2 months in patients receiving bendamustine in combination with rituximab and those receiving R-CHOP, respectively.[10001] A progression-free survival benefit was observed for the bendamustine-rituximab regimen compared with R-CHOP in subset analyses in patients with mantle cell lymphoma, follicular lymphoma, and Waldenstrom macroglobulinemia, but not in those with marginal-zone lymphoma.[10001] Overall response rates were similar in patients receiving bendamustine in combination with rituximab and those receiving R-CHOP (93 versus 91%, respectively); however, the complete response rate was higher in the bendamustine-rituximab group (40 versus 30%).[10001] Although median overall survival had not been reached in either group at the time of analysis, substantial differences were not observed between the treatment groups.[10001] Subgroup analysis suggested that the progression-free survival benefit observed for the bendamustine-rituximab regimen was independent of age, serum LDH concentration, and Follicular Lymphoma International Prognostic Index (FLIPI) score; however, statistical significance was not reached for elevated serum LDH concentration or unfavorable FLIPI score.[10001] Although erythematous (16 versus 9%) or allergic (15 versus 6%) skin reactions occurred more frequently in patients receiving bendamustine in combination with rituximab, serious adverse effects (19 versus 29%), grade 3 or 4 leukopenia (37 versus 72%), grade 3 or 4 neutropenia (29 versus 69%), alopecia (0 versus 100%), paresthesia (7 versus 29%), stomatitis (6 versus 19%), infection (37 versus 50%), and sepsis (less than 1 versus 3%) occurred more frequently in those receiving R-CHOP.[10001]

The second study (BRIGHT) was a phase 3, open-label, randomized, noninferiority study in which 447 patients received 6–8 cycles of therapy with either bendamustine in combination with rituximab or standard combination chemotherapy (R-CHOP or rituximab plus cyclophosphamide, vincristine, and prednisone [R-CVP]).[10018] Patients with previously untreated mantle cell lymphoma or CD20-positive indolent NHL, including the histologic subtypes follicular lymphoma (grade 1 or 2), Waldenstrom macroglobulinemia, and marginal-zone lymphoma, were eligible for enrollment in the study.[10018] Patients receiving the bendamustine-rituximab regimen received rituximab 375 mg/m^2 IV on day 1 and bendamustine hydrochloride 90 mg/m^2 IV daily on days 1 and 2 of each 28-day cycle.[10018] Those receiving R-CHOP received rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, doxorubicin hydrochloride 50 mg/m^2 IV, and vincristine sulfate 1.4 mg/m^2 (up to 2 mg) IV on day 1, followed by prednisone 100 mg daily on days 1–5 of each 21-day cycle, while those receiving R-CVP received rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 (option of 1 g/m^2) IV, and vincristine sulfate 1.4 mg/m^2 (up to 2 mg) IV on day 1, followed by prednisone 100 mg daily on days 1–5 of each 21-day cycle.[10018] The median patient age was about 60 years (range: 25–86); about 68% of patients had stage IV disease, 22% had stage III disease, 70% had follicular lymphoma, and 17% had mantle cell lymphoma.[10018] The primary measure of efficacy was the rate of complete response, as defined by the International Working Group (IWG) criteria and assessed by a blinded independent review committee.[10018]

Bendamustine in combination with rituximab was noninferior to R-CHOP and R-CVP for attainment of complete response; complete response was achieved in 31% of patients receiving bendamustine in combination with rituximab compared with 25% of those receiving R-CHOP or R-CVP.[10018] Although complete response rates in patients with indolent NHL (mainly follicular lymphoma) tended to favor the bendamustine-rituximab regimen over R-CHOP or R-CVP, subset analysis failed to establish noninferiority of the bendamustine-rituximab regimen in patients with indolent NHL or follicular lymphoma.[10018] In the subset of patients with mantle cell lymphoma, complete response rates were higher in patients receiving bendamustine in combination with rituximab compared with those receiving R-CHOP or R-CVP.[10018] Overall response rates were higher in patients receiving bendamustine in combination with rituximab compared with those receiving R-CHOP or R-CVP (97 versus 91%).[10018] Follow-up to establish long-term efficacy is ongoing for this study.[10018] Hypersensitivity reactions, vomiting, and nausea occurred more frequently in patients receiving bendamustine in combination with rituximab, while peripheral neuropathy, paresthesia, alopecia, constipation, and grade 3 or 4 leukopenia or neutropenia occurred more frequently in patients receiving R-CHOP and/or those receiving R-CVP.[10018] Although use of type 3 serotoninergic (5-HT$_3$) receptor antagonists was similar in all treatment groups, concomitant use of aprepitant was more common in patients receiving R-CHOP than in those receiving bendamustine in combination with rituximab or those receiving R-CVP.[10018]

Based on current evidence,[10001, 10018] use of bendamustine in combination with rituximab may be considered a reasonable choice (accepted, with possible conditions) for the treatment of previously untreated advanced-stage indolent NHL or mantle cell lymphoma; however, the histologic subtype of NHL should be considered when selecting a combination chemotherapy regimen.

Dosage:

When bendamustine has been used in combination with rituximab† in adults with previously untreated† advanced-stage indolent NHL or previously untreated advanced-stage mantle cell lymphoma†, rituximab 375 mg/m^2 has been administered by IV infusion on day 1, followed by IV infusion (over 30–60 minutes) of bendamustine hydrochloride 90 mg/m^2 on days 1 and 2.[10001, 10018] The bendamustine-rituximab regimen has been administered on a 28-day cycle for up to 8 cycles.[10001, 10018]

References:

10001. Rummel MJ, Niederle N, Maschmeyer G 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.* 2013; 381:1203-10.

10018. Flinn IW, van der Jagt R, Kahl BS 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; 123:2944-52.

Oncology Expert Committee Voting Results:

Proposed Level of Evidence: Level 2 (Moderate strength/quality); progression-free survival

Concur with rating: 5 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 2 votes

Reasonable choice (Accepted, treatment option): 3 votes

Not fully established (Unclear risk/benefit or equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Proposed Consensus Recommendation:

Based on current evidence, use of bendamustine in combination with rituximab may be considered a reasonable choice (accepted, with possible conditions) for the treatment of previously untreated advanced-stage indolent NHL or mantle cell lymphoma; however, the histologic subtype of NHL should be considered when selecting a combination chemotherapy regimen.

Concur with recommendation: 5 votes

Do not concur with recommendation: 0 votes

Oncology Expert Committee Members' Comments:

Comments in Support of Vote on Level of Evidence and Grade of Recommendation:

Reviewer #1: [Specific patient population] Marginal-zone lymphoma.
[Specific patient population] NHL: limited benefit in marginal-zone lymphoma p-value = 0.3249.

Comments on Draft Narrative Summary:

Reviewer #1: Need to call out decreased response in marginal-zone lymphoma.

Comments on Proposed Consensus Recommendation:

None.

Participants:

AHFS Staff Members (writing and editing): Lily Leu, Pharm.D., BCOP; Jane Miller, Pharm.D.

AHFS Oncology Expert Committee Members (reviewing and voting): Beth Faiman, Ph.D., RN, ANP-BC, AOCN; Raymond Hohl, M.D., Ph.D.; LeAnne Kennedy, Pharm.D., BCOP; Sandra Kurtin, RN, MS, AOCN, ANP-C; LeAnn Norris, Pharm.D., BCPS, BCOP

External Consultants: None

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

Publication Date: May 24, 2016