Original Study

Differences in Quality of Life Between Bendamustine-Rituximab and R-CHOP/R-CVP in Patients With Previously Untreated Advanced Indolent Non-Hodgkin Lymphoma or Mantle Cell Lymphoma

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Abstract

Comparative chemotherapy-related quality of life data are lacking. Bendamustine-rituximab (BR) demonstrated noninferiority to R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone)/R-CVP (rituximab/cyclophosphamide/vincristine/prednisone) in first-line advanced indolent non-Hodgkin and mantle cell lymphomas. Patients receiving BR reported improvement across many domains, with a few exceptions, of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

Background: We previously reported results of the phase III, randomized, noninferiority trial comparing bendamustine-rituximab (BR) with standard R-CHOP (rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone)/R-CVP (rituximab/cyclophosphamide/vincristine/prednisone) in previously untreated advanced indolent non-Hodgkin and mantle cell lymphomas. Here we report health-related quality of life (HRQOL) results from the trial. **Methods:** HRQOL, as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), was a secondary end point. Differences between group means in global health status (GHS), 5-item functioning, and 9 symptoms/single-item measures at week 1 of cycle 1 and end-of-cycles 3 and 6 were examined using the screening (baseline) score as a covariate in analysis of covariance. **Results:** Overall EORTC QLQ-C30 compliance was 75.2%, 89.5%, and 89.9% at week 1 of cycle 1 and end-of-cycles 3 and 6,

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respectively. Patients treated with BR reported improvements in Cognitive Functioning, Physical Functioning, Social Functioning, Emotional Functioning, and GHS as well as reduction in dyspnea, constipation, and fatigue at some, but not all, time points. Patients treated with standard therapy reported less nausea/vomiting at one time point. **Conclusion:** Compared with patients treated with standard therapy, patients treated with BR reported better quality of life in several areas.

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Introduction

The impact of cancer treatment on health-related quality of life (HRQOL) has been increasingly considered in regulatory and clinical decision-making. Studies have found higher psychological distress associated with low functioning scores on HRQOL instruments, and these effects can be seen years after completion of cancer therapy.[1,2]

Patient-reported outcomes (PROs) can provide a valuable perspective on treatment tolerability.[3,4] In addition to the disease-associated symptoms patients experience, chemotherapy treatment of non-Hodgkin lymphoma (NHL) can be physically and emotionally taxing, as shown by 3 PRO assessments in a study of 222 follicular lymphoma patients, as well as by 3 quality of life (QOL) questionnaires in a study of 132 elderly patients with aggressive NHL.[5,6] The clinical importance of HRQOL in evaluating the tolerability effects of various treatment regimens in advanced cancer was highlighted by the recent publication of PRO results of patients with advanced cervical cancer and poor prognosis in a "practice-changing" phase 3 study, in which improvements in both overall survival and progression-free survival (PFS) related to the addition of a new agent to chemotherapy were not accompanied by a decline in HRQOL.[7] Despite the importance of HRQOL during cancer treatment, there are few data comparing treatment regimens for impact on HRQOL in NHL.

Our recent randomized, open-label, phase III, global trial demonstrated noninferiority of complete response rate (primary objective) between bendamustine-rituximab (BR) and standard rituximab-based chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] or rituximab, cyclophosphamide, vincristine, and prednisone [R-CVP]) in first-line treatment of patients with indolent NHL or mantle cell lymphoma (MCL) (31% vs. 25%, respectively; $P = .0225$ for noninferiority).[8] In the open-label, randomized, multicenter, phase III, noninferiority Study group indolent Lymphomas (StiL) trial, PFS was significantly longer for BR therapy versus standard R-CHOP in treatment-naive patients with MCL or indolent NHL (at median follow-up of 45 months, median PFS was 69.5 vs. 31.2 months, respectively; $P < .0001$ for superiority).[9]

At present, all 3 treatment regimens (BR, R-CHOP, and R-CVP) are recommended first-line treatments for follicular lymphoma.[10] HRQOL data for these regimens could help physicians choose the best treatment regimen. In a recent cost-utility analysis using EQ-5D utility scores from a follicular lymphoma study, the clinical benefits of BR observed in the StiL study and in a patient-simulated model translated into 7.19 total quality-adjusted life-years (QALYs) versus 6.46 for R-CHOP and 6.58 for R-CVP, a gain of 0.73 and 0.61 QALYs, respectively.[9,11,12]

In this report, we analyzed HRQOL data, as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), collected during the Bendamustine Rituximab InvestiGational non-Hodgkin's Trial (BRIGHT).[8]

Patients and Methods

The study design, enrollment eligibility, exclusion criteria, treatment plan, and efficacy/safety results of the BRIGHT trial have been reported in detail elsewhere.[8] To summarize, the BRIGHT trial was a randomized, multicenter, open-label, active-controlled, phase III study that was conducted to compare the efficacy and safety of intravenous combination therapy of bendamustine (90 mg/m^2/day on days 1 and 2) and rituximab (375 mg/m^2 on day 1) in 28-day cycles with that of R-CHOP/R-CVP for six 21-day cycles in the treatment of treatment-naive patients with advanced, CD20-positive indolent NHL or MCL. Patients were preassigned by investigators to a standard treatment (R-CHOP or R-CVP) at screening; patients were then randomly assigned to a standard treatment or BR for 6 cycles (up to 8 cycles at investigator discretion).[8] Eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2; estimated life expectancy of ≥ 6 months; and adequate renal, hepatic, and hematologic function. The primary end point was the proportion of patients with complete response at the end of treatment.[8] Among the secondary outcome measures were QOL and the incidence of adverse events (AEs) throughout treatment.[8] The study protocol was approved by institutional review boards at all institutions that participated. Written informed consent was provided by all patients who enrolled in this trial.[8] The BRIGHT study is registered with ClinicalTrials.gov (identifier: NCT00877006).

Procedures for HRQOL and Safety Data Collection

The EORTC QLQ-C30 is a standardized tool that incorporates a global health status (GHS)/QOL scale, 5 functional scales (physical, role, emotional, cognitive, and social), 3 symptom scales (fatigue, nausea/vomiting, and pain), and 6 single-item measures (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact); all scores could range from 0 to 100, with rising scores on functional and GHS/QOL scales indicating improvement and rising scores on symptom/single-item scales indicating worsening.[13] Patients completed the EORTC QLQ-C30 form at baseline, week 1