R-High-CHOP/CHASER/LEED with autologous stem cell transplantation in newly diagnosed mantle cell lymphoma: JCOG0406 STUDY


Although induction immunochemotherapy including high-dose cytarabine and rituximab followed by high-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) is recommended for younger patients (≤65 years old) with untreated mantle cell lymphoma (MCL), no standard induction and HDC regimen has been established. We conducted a phase II study of induction immunochemotherapy of R-High-CHOP/CHASER followed by HDC of LEED with ASCT in younger patients with untreated advanced MCL. Eligibility criteria included untreated MCL, stage II bulky to IV, and age 20-65 years. Patients received 1 cycle of R-High-CHOP followed by 3 cycles of CHASER every 3 weeks. Peripheral blood stem cells (PBSC) were harvested during CHASER. LEED with ASCT was delivered to patients who responded to R-High-CHOP/CHASER. Primary endpoint was 2-year progression-free survival (PFS). From June 2008 to June 2012, 45 patients (median age 59 years; range 38-65 years) were enrolled. PBSC were successfully harvested from 36 of 43 patients. Thirty-five patients completed ASCT. Two-year PFS was 77% (80% CI 68-84), which met the primary endpoint. Five-year PFS and overall survival were 52% (95% CI 34-68%) and 71% (95% CI 51-84%), respectively. Overall response and complete response rates after induction immunochemotherapy were 96% and 82%, respectively. The most common grade 4 toxicities were hematological. In younger patients with untreated MCL, R-High-CHOP/CHASER/LEED with ASCT showed high efficacy and acceptable toxicity, and it can now be considered a standard treatment option.

KEYWORDS
autologous stem cell transplantation, cytarabine, high-dose chemotherapy, mantle cell lymphoma, rituximab

1 | INTRODUCTION

Mantle cell lymphoma (MCL) is a well-recognized B-cell lymphoma subtype that accounts for approximately 5% of all patients with NHL.1 The clinical course of MCL ranges from indolent to aggressive, with a poor prognosis and a median OS of about 3-5 years with conventional chemotherapy.2,3 The prognosis when using conventional chemioimmunotherapy remains poor. Two-year PFS of 30% was reported in a phase II study of MCL patients treated with 6 cycles of rituximab, an anti-CD20 antibody, and CHOP chemotherapy.4

However, a randomized phase III study by the European MCL Network that compared myeloablative radiochemotherapy followed by ASCT with interferon-α (IFN-α) maintenance during the first remission after a CHOP-like regimen demonstrated significant superiority of ASCT, with PFS of 45% in younger patients aged 65 years or less in patients with advanced-stage MCL.5 Promising approaches to improving CR rate before ASCT, as well as PFS and OS, include modulated induction therapy with HDAC-based chemotherapy regimens and rituximab. These strategies are based on clinical studies in which the addition of rituximab to an HDAC-containing regimen was reported to ensure tumor depletion in vivo while allowing the collection of PBSC with conserved engraftment capability that was devoid of tumor cells.6,7

A phase II MCL-2 study by the Nordic Lymphoma Group including HDAC and rituximab prior to stem cell mobilization, followed by HDC and ASCT, demonstrated an excellent ORR (96%), with a CR rate of 56%, and PFS of 70% and OS of 70% after 6 years.8 Similar promising results were also reported in another phase II study of an induction regimen with R-CHOP and R-DHAP followed by ASCT, which was conducted by GELA.9 This regimen of 6 cycles of alternating R-CHOP/R-DHAP followed by consolidative HDC with ASCT resulted in a superior PFS compared with the regimen of 6 cycles of R-CHOP followed by consolidative HDC with ASCT reported for a randomized phase III study by the European Mantle Cell Network (European MCL Network).10 Recently, rituximab maintenance after ASCT was shown to improve event-free survival, PFS, and OS in