LymphomaHub

MCL

Rituximab, bendamustine, and low-dose cytarabine induction shown to be an effective and safer induction therapy for elderly MCL patients

Karl Kemp-O'Brien | Jan 23, 2017

This month in The Lancet Haematology, Carlo Visco, from San Bortolo Hospital, Vicenza, Italy, and colleagues from the Fondazione Italiana Linformi (FIL) published the results of a single-arm, multicenter, phase II, trial of elderly MCL patients treated with low-dose cytarabine (500 mg/m^2), rituximab and bendamustine (RBAC500)[1]. The study recruited MCL patients older than 65 years from 29 Italian centers, totaling 57 patients all of whom received at least two cycles of treatment.

Key Highlights:

- RBAC500 treatment: Six 4-week cycles of I.V. rituximab (374 mg/m^2 Day 1), bendamustine (70 mg/m^2 Day 2 and 3), and cytarabine (500 mg/m^2 Day 2–4, 2 hrs after bendamustine)
- 100% pts received 2 cycles, 95% received 4 cycles, 67% received 6 cycles
- 91% of pts achieved CR at treatment end
- 2-year OS was 86%
- 2-year PFS was 81%, and 76% with a median follow-up of 35 months
- 72% pts had a reduction in dose during treatment, with 25% pts not having any dose-reduction or delay in cycles
- 40% pts had at least one 'relevant toxicity'
- Most frequent grade 3–4 AEs: thrombocytopenia, neutropenia, and leukopenia (52%, 49%, and 44% of cycles, respectively)
- No patient deaths due to treatment reported
- Ki67 expression was a strong predictive marker for PFS and OS, consistent with other studies

The authors concluded that, in comparison with a previous trial[2], reducing the dose of cytarabine resulted in lower rates of high grade hematological AEs while still being an effective treatment. The CR rates in particular for RBAC500 (91%) compare favorably with and improve upon the results achieved through rituximab-bendamustine treatment alone (30–40%)[3,4]. In conclusion, the authors stated that RBAC500 was an effective treatment for elderly MCL patients that did not require expensive maintenance therapy, and the reported hematological toxicities rates, while high, were manageable. Phase III trials will be required to confirm these findings, but early data is promising.

References:

1. **Visco C. *et al.* Rituximab, bendamustine, and low-dose cytarabine as induction therapy in elderly patients with mantle cell lymphoma: a multicentre, phase 2 trial from Fondazione Italiana Linfomi. The Lancet Haematology. Jan**

2017; 4(1):e15-e23. DOI: 10.1016/S2352-3026(16)30185-5.

2. **Visco C. *et al.* Combination of rituximab, bendamustine, and cytarabine for patients with mantle-cell non-Hodgkin lymphoma ineligible for intensive regimens or autologous transplantation. Journal of Clinical Oncology. Apr 2013; 31: 1442–1449. DOI: 10.1200/JCO.2012.45.9842.**
3. **Flinn I.W. *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. May 2014; 123: pp. 2944-2952. DOI:https://doi.org/10.1182/blood-2013-11-531327**
4. **Rummel M. *et al.* Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised , open-label, non-inferiority phase 3 trial. Lancet Oncology. Jan 2016; 17: pp. 57-66. DOI: 10.1016/S1470-2045(15)00447-7**

Abstract:

Background. The combination of rituximab, bendamustine, and cytarabine (R-BAC) was highly active in a pilot trial of mantle cell lymphoma, but its use was restricted by high haematological toxicity. We aimed to assess the efficacy and safety of an R-BAC regimen with low-dose cytarabine (RBAC500).

Methods. In this multicentre, phase 2 trial, we recruited previously untreated patients with an established histological diagnosis of mantle cell lymphoma from 29 Fondazione Italiana Linfomi centres in Italy. Patients had to be older than 65 years and fit according to the comprehensive geriatric assessment, or aged 60–65 years if they were ineligible for high-dose chemotherapy plus autologous stem-cell transplantation and were fit or unfit. All patients received RBAC500 (rituximab 375 mg/m2 on day 1, bendamustine 70 mg/m2 on days 2 and 3, and cytarabine 500 mg/m2 on days 2–4; all administered intravenously) every 4 weeks for up to six cycles. Primary endpoints were the proportion of patients achieving complete response at the end of treatment and toxicity, defined as the occurrence of any of the stop treatment criteria or of any episode of relevant toxicity. All patients who started at least one cycle of RBAC500 were included in the primary and safety analyses. Using efficacy and toxicity as a composite primary endpoint, we considered the final conclusion positive if more than 28 of 57 patients achieve complete response and fewer than 18 of 57 patients report toxicities. This study is registered with EudraCT, number 2011-005739-23, and ClinicalTrials.gov, number NCT01662050, and is completed.

Findings. Between May 2, 2012, and Feb 25, 2014, we enrolled 57 patients (median age 71 years, IQR 67–75). 54 (95%) patients received at least four RBAC500 cycles (three discontinued because of toxicity), and 38 (67%) completed six cycles. Two (4%) had disease progression (one after the fourth cycle and one after the sixth cycle). All 52 (91%, lower limit of one-sided 95% CI 85%) remaining patients achieved complete response at the end of treatment. 23 (40%, upper limit of one-sided 95% CI 53%) of 57 patients had at least one episode of relevant toxicity. The most frequent grade 3–4 haematological toxicities were neutropenia (149 [49%] of 304 cycles) and thrombocytopenia (158 [52%]). Most treatment-related non-haematological adverse events were of grade 1–2, with the most frequent ones being fatigue (14 [25%] patients), nausea or vomiting (12 [21%]), and infusion-related reactions or tumour lysis syndrome (12 [21%]). 41 (72%) patients required a dose reduction. 12 patients died during the study, but no deaths were related to treatment.

Interpretation. RBAC500 is an effective treatment for elderly patients with mantle cell lymphoma and, despite not meeting our prespecified safety boundary, haematological toxicity was manageable with appropriate supportive care and dose reduction. Since maintenance therapy is not required, RBAC500 could be considered an option and should be studied in phase 3 trials.