DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) IN ELDERLY PATIENTS

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TRIAL SUMMARY: Lenalidomide vs placebo as maintenance therapy in patients with DLBCL following R-CHOP induction

Thieblemont C, Tilly H, Gomez da Silva M, et al. First analysis of an international double-blind randomized phase III study of lenalidomide maintenance in elderly patients with DLBCL treated with R-CHOP in first line, the REMARC study from LYSA. ASH Annual meeting, San Diego, California, December 4, 2016, Abstract 471.

The REMARC study is an international, multicenter, double-blind, randomized, placebo-controlled, phase 3 trial that assessed the benefit of lenalidomide (LEN) maintenance after response to R-CHOP in older patients with untreated diffuse large B-cell lymphoma (DLBCL), follicular lymphoma grade 3B (FL3B) or transformed lymphoma. Patients achieving CR or PR at the end of 6 or 8 cycles of R-CHOP21 or R-CHOP14 were stratified by CR/PR status and country, and randomized 1:1 to receive 2 years of LEN maintenance (25 mg/day for 21 of every 28 days) or placebo (PBO). The primary endpoint of the study was PFS. Secondary endpoints were safety, PR to CR conversion rate, and OS.

Results: With a median followup of 40 months, median PFS (according to independent centralized radiology review) was not reached in the LEN group vs 68 months in the PBO group (hazard ratio favouring the LEN group, 0.708; 95% CI, 0.537–0.932; p=0.0135). In the LEN group, 18 patients (21%) converted from PR to CR during maintenance compared to 13 patients (14%) in the PBO group. Immature OS data did not show any benefit for LEN arm, a lack of difference not attributable to an excess of lymphoma relapse, secondary cancer or safety problems in the LEN arm. The most common observed grade 3 or 4 adverse events (AEs) were neutropenia (56% vs 22%), rash (5% vs 1%), infections (8% vs 6%), and thrombocytopenia (2.5% vs 0.6%) in LEN and PBO arms, respectively. Secondary primary malignancies occurred in 33 patients receiving LEN and in 42 patients on PBO.

COMMENTARY: Approximately 65% of patients suffering from DLBCL are cured by R-CHOP. Recent efforts to increase this cure rate have involved combining R-CHOP with novel agents that impact germinal centre B-cell (GCB) or activated B-cell (ABC) subtype molecular signalling pathways. Unfortunately, results of such studies have thus far proved disappointing. These negative studies have included the addition of bevacizumab (MAIN, stopped due to toxicity) or bortezomib (PYRAMID)[1] to R-CHOP, or the use of enzastaurin (PRELUDE)[2] or everolimus (PILLAR-2)[3] following R-CHOP. Results of 2 other important but negative phase 3 trials were reported at ASH 2016. These were the CALGB/Alliance50303[4] and the GOYA[5] trials, which demonstrated no superiority of dose-adjusted EPOCH-R (doxorubicin, etoposide, vincristine, cyclophosphamide, prednisone, rituximab) or obinutuzumab-CHOP over conventional R-CHOP, respectively.

Although all of these trials were negative, it is important to recognize that they did not study particularly poor prognosis patients. This likely occurred because of: 1) restrictive eligibility criteria such as ECOG=0-1; 2) lengthy screening and recruitment procedures that essentially prevented accrual of patients with rapidly progressive, symptomatic, high tumour burden disease; or 3) because of late randomization only of patients who achieved CR to induction therapy. Ongoing studies evaluating the addition of novel agents to R-CHOP include ibrutinib-R-CHOP and lenalidomide-R-CHOP (ROBUST study) for non-GCB/ABC DLBCL.

In contrast to the above negative studies, the REMARC randomized, double-blind, placebo-controlled phase 3 trial of lenalidomide (LEN) maintenance for 2 years following R-CHOP in DLBCL patients 60 to 80 years of age demonstrated a significant improvement in PFS for all randomized patients, (HR, 0.708; 95% CI, 0.537–0.933; p=0.0135).[6] This PFS benefit included patients with CR (HR, 0.722; 95% CI, 0.521–0.999) as well as those without CR after R-CHOP (HR, 0.592; 95% CI, 0.365–0.959). Interestingly, LEN trended toward prolonging PFS in GCB-positive DLBCL (p=0.0742) but not ABC or unclassified disease, despite prior studies that reported preferential activity of LEN in non-GCB types of DLBCL.[7,8] There was no significant difference in OS for patients treated with LEN vs placebo (HR, 1.218; 95% CI, 0.861–1.721; p=0.264), seemingly explained by higher ASCT rates in patients who relapsed in the placebo arm than those who relapsed in the LEN arm. Lower ASCT rates after LEN might theoretically have been due to less chemosensitivity, more frequent stem cell mobilization failure, or unresolved toxicity. Overall, treatment was discontinued

due to toxicity in 36% vs 16%, 1 or more dose reductions were required in 72% vs 42%, and grade 3-4 neutropenia occurred in 56% vs 22% of LEN vs placebo patients, respectively.

If the final published report of the REMARC study confirms that LEN maintenance improves PFS for elderly DLBCL patients after R-CHOP, it would be a reasonable treatment approach, especially for those patients who are not considered good candidates for intensive salvage therapy and ASCT if relapse were to occur after R-CHOP alone.

IN BRIEF

Already known

- Efforts to improve the cure rate for diffuse large B-cell lymphoma by combining R-CHOP with novel agents have been disappointing so far.

What this trial showed

- Preliminary results from the REMARC study showed that, among older patients, lenalidomide maintenance following R-CHOP increased progression-free survival (PFS) for patients with and without complete response after R-CHOP.
- Toxicity led to treatment discontinuation in 36%, and dose reduction in 72% of patients receiving lenalidomide maintenance.

Next steps

- Wait for published reports from REMARC. If these confirm improved PFS, consider lenalidomide maintenance after R-CHOP for elderly patients with few options in case of relapse.

References

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