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DLBCL

Long-term follow-up of R-CHOP21 and lenalidomide in DLBCL: Analysis of two phase II trials

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On 8 November, Alessia Castellino and colleagues, published in *Blood Cancer Journal* the results of a long-term follow-up analysis from two phase II trials conducted by the Mayo Clinic, USA (MC078E) and the Italian Lymphoma Foundation, IT (REAL07).

The trials investigated the efficacy and safety of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) plus lenalidomide treatment in newly-diagnosed untreated patients with diffuse large B-cell lymphoma (DLBCL). Both trials reported a feasible and effective profile for R-CHOP and lenalidomide with an overall response rate (ORR) higher than 90%. The aim of this study was to report the long-term follow-up outcomes of this treatment from these two independent phase II trials. The primary endpoints of this analysis were progression-free survival (PFS), time to progression (TTP), overall survival (OS) and safety.

Study designs

- Patients with newly-diagnosed histologically-confirmed $CD20^+$ DLBCL, Ann Arbor stage II-IV and Eastern Cooperative Oncology Group (ECOG) performance status 0–2
- N = 112 patients (MC078E, 63; REAL07, 49) were included in this long-term follow-up analysis
- Median age (range) = 69 (22–87) years
- Median follow-up = 5.1 years
- Main differences between the two trials:
  - MC078E included all patients older than 18 years old without an upper age limit and all International Prognostic Index (IPI) risk scores
  - REAL07 included patients between 60 and 80 years old and only with IPI ≥ 2
- Dosing:
  - All patients received R-CHOP for 21 days (R-CHOP21) together with lenalidomide
  - Rituximab: 375mg/m^2, cyclophosphamide: 750 mg/m^2, doxorubicin: 50 mg/m^2, vincristine: 1.4 mg/m^2 (capped at 2 mg), all on Day 1, prednisone 100 mg/m^2 (MC078E) or 40 mg/m^2 (REAL07) per day on Days 1 through 5, given every 21 days)
  - Lenalidomide: 25 mg/day for 10-day cycles, while 15 mg/day for 14-day cycles
  - Total cumulative lenalidomide dosing: 250 mg/m^2 (MC078E) and 210 mg/m^2 (REAL07), respectively

Results

- At a median follow-up of 5.1 years:

- Five-year PFS: 59% (95% CI, 48–73) for the MC078E *vs* 69% (95% CI, 57–85) for the REAL 07 trial ($P = 0.09$)
- Five-year OS: 74% (95% CI, 63–865) in the MC078E *vs* 77% (95% CI, 64–92) in the REAL07 trial ($P = 0.28$)
- Five-year TTP: 68% (95% CI, 57–81) in the MC078E *vs* 72% (95% CI, 60–88) in the REAL07 trial ($P = 0.24$)

- For the whole cohort together at a median follow-up of 5.1 years:
  - Five-year PFS: 63.5% (95% CI, 54.7–73.6)
  - Five-year OS: 75.4% (95% CI, 67.3–84.5)
  - Five-year TTP: 70.1%% (95% CI, 61.6–79.9)
- A total of 32 relapse cases were observed (two, CNS relapses)
- Outcomes from cell-of-origin (COO) stratified analysis for germinal center B-cell (GCB) *vs* non-GCB patients:
  - Five-year PFS: 52.8% (95% CI, 39.8–70.2) *vs*5% (95% CI, 51.1–81.5; $P = 0.198$)
  - Five-year TTP: 61.6% (95% CI, 48.1–78.9) *vs*6% (95% CI, 56.6–85.7; $P = 0.444$)
  - Five-year OS: 68.6% (95% CI, 56.1–83.9) *vs*1% (95% CI, 61.3–89.7; $P = 0.238$)
- No significant differences between PFS, ITT or OS were observed between patients with IPI 0–2 and 3–5, as assessed by subgroup analysis

Safety

- Only one toxic death was recorded during the follow-up (sepsis)
- Three patients experienced a serious Grade 4 late toxicity
- Other reported adverse events (AEs) ≤ Grade 3 included:
  - Infections
  - Thrombosis
  - Persistent neuropathy
  - Cardiovascular disease
- The following secondary malignancies were observed in n = 7 patients (6.3%) with a median time to onset 16.4 months after the end of the treatment:
  - Therapy-related acute myeloid leukemia (n = 1)
  - Non-therapy related tumors (n = 6)
  - Lymphoma (n = 2)
  - Metastatic adenocarcinoma of unknown origin (n = 1)
  - Prostatic cancer (n = 1)
  - Rectal adenocarcinoma (n = 1)
  - Non-melanotic tumor (n = 1)

This long-term follow-up analysis of two phase II trials on newly-diagnosed DLBCL patients, indicates that R-CHOP21 together with lenalidomide maintain a high efficacy over the years with very good PFS, OS and ITT rates. This combination treatment seems to also be tolerable and safe up to a five-year follow-up, with a very low incidence of secondary malignancies.

References

1. Castellino A. *et al.* Lenalidomide plus R-CHOP21 in newly diagnosed diffuse large B-cell lymphoma (DLBCL): long-term follow-up results from a combined analysis from two phase 2 trials. *Blood Cancer J.* 2018 Nov 8;8(11):108. DOI: 10.1038/s41408-018-0145-9.