LymphomaHub

HL

GHSG HD18: Addition of rituximab to BEACOPPescalated does not improve newly diagnosed, advanced, aggressive HL patient outcome

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In February, in The Lancet Oncology, Peter Borchmann, from the First Department of Internal Medicine, University Hospital of Cologne, Cologne, Germany, and colleagues in the German Hodgkin Study Group (GHSG) published the second planned, but final, interim analysis of an international, multicenter, phase III study into using PET to identify PET2-positive advanced, aggressive Hodgkin Lymphoma (HL) patients. FDG-PET was performed after two rounds of the GHSG standard treatment of $BEACOPP_{escalated}$ and was centrally reviewed. Patients who were classified as PET2-positive were then given either $BEACOPP_{escalated}$, or $BEACOPP_{escalated}$ with the addition of rituximab, with the goal being eight cycles of $BEACOPP_{escalated}$ in total.

Key highlights:

- Recruited 1,100 pts, 440 PET2-positive patients randomized: $BEACOPP_{escalated}$ = 220 pts, R-$BEACOPP_{escalated}$ = 220 pts
- Treatment:
  - $BEACOPP_{escalated}$ followed the standard GSHG protocol
  - IV rituximab 375mg/m^2 (700mg max dose) on Cycle 4 D0, Cycle 4 D3, then D1 of Cycles 5–8
- Median follow-up = 33 months
- Estimated 3-year PFS
  - $BEACOPP_{escalated}$ = 91.4% (95% CI, 0–95.7)
  - R-$BEACOPP_{escalated}$ = 93% (95% CI, 4–96.6)
  - *P* = 0.99
- Estimated 3-year OS
  - $BEACOPP_{escalated}$ = 96.5% (95% CI,93.6–99.3)
  - R-$BEACOPP_{escalated}$ = 94.4% (95% CI, 90.8–97.9)
  - *P* = 0.31
- Severe AEs ≥Grade 3:
  - $BEACOPP_{escalated}$ = 23% pts
  - R-$BEACOPP_{escalated}$ = 20% pts
- In total, 6 $BEACOPP_{escalated}$ pts died, 10 R-$BEACOPP_{escalated}$ pts died (3% and 5%, respectively)
- Treatment-related deaths (infection): 1 $BEACOPP_{escalated}$ pt, 3 R-$BEACOPP_{escalated}$ pts

In conclusion, the authors stated that there was no difference in outcome for PET2-positive patients given rituximab in addition to $BEACOPP_{escalated}$. When these results were compared to PET2-unselected patients in previous GHSG trials, it was shown that PET2 is not a suitable prognostic indicator for newly-diagnosed advanced stage HL patients.

Reference:

1. Borchmann P. *et al.* Progression-free survival of early interim PET-positive patients with advanced stage Hodgkin's lymphoma treated with BEACOPPescalated alone or in combination with rituximab (HD18): an open-label, international, randomised phase 3 study by the German Hodgkin Study Group. The Lancet Oncology. 2017 Feb 21. DOI: 10.1016/S1470-2045(17)30103-1. [Epub ahead of print: 2017 Feb 21].

Abstract:

Background. Advanced stage Hodgkin's lymphoma represents a heterogeneous group of patients with different risk profiles. Data suggests that interim PET assessment during chemotherapy is superior to baseline international prognostic scoring in terms of predicting long-term treatment outcome in patients with Hodgkin's lymphoma. We therefore hypothesised that early interim PET-imaging after two courses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) might be suitable for guiding treatment in patients with advanced stage Hodgkin's lymphoma. We aimed to assess whether intensifying standard chemotherapy (BEACOPPescalated) by adding rituximab would improve progression-free survival in patients with positive PET after two courses of chemotherapy. Methods. In this open-label, international, randomised, phase 3 study, we recruited patients aged 18–60 years with newly diagnosed, advanced stage Hodgkin's lymphoma from 160 hospitals and 77 private practices in Germany, Switzerland, Austria, the Netherlands, and the Czech Republic. Interim PET-imaging was done after two cycles of BEACOPPescalated and centrally assessed by an expert panel. Patients with a positive PET after 2 cycles of BEACOPPescalated chemotherapy (PET-2) were randomly assigned (1:1) to receive six additional courses of either BEACOPPescalated (BEACOPPescalated group) or BEACOPPescalated plus rituximab (R-BEACOPPescalated group). PET-2 was assessed using a 5-point scale with 18FDG uptake higher than the mediastinal blood pool (corresponding to Deauville scale 3) defined as positive. BEACOPPescalated was given as previously described; rituximab was given intravenously at a dose of 375 mg/m2 (maximum total dose 700 mg), the first administration starting 24 h before starting the fourth cycle of BEACOPPescalated (day 0 and day 3 in cycle 4, day 1 in cycles 5–8). Randomisation was done centrally and used the minimisation method including a random component, stratified according to centre, age, stage, international prognostic score, and sex. The primary efficacy endpoint was 5 year progression-free survival, analysed in the intention-to-treat population. We are reporting this second planned interim analysis as the final report of the trial. The trial is registered with ClinicalTrials.gov, number NCT00515554. Findings. Between May 14, 2008, and May 31, 2011, we enrolled 1100 patients. 440 patients had a positive PET-2 and were randomly assigned to either the BEACOPPescalated group (n=220) or the R-BEACOPPescalated group (n=220). With a median follow-up of 33 months (IQR 25–42) for progression-free survival, estimated 3 year progression-free survival was 91·4% (95% CI 87·0–95·7) for patients in the BEACOPPescalated group and 93·0% (89·4–96·6) for those in the R-BEACOPPescalated group (difference 1·6%, 95% CI −4·0 to 7·3; log rank p=0·99). Common grade 3–4 adverse events were leucopenia (207 [95%] of 218 patients in the BEACOPPescalated group vs 211 [96%] of 220 patients in the R-BEACOPPescalated group), and severe infections (51 [23%] vs 43 [20%] patients). Based on a futility analysis, the independent data monitoring committee recommended publication of this second planned interim analysis as the final result. Six (3%) of 219 patients in the BEACOPPescalated group and ten (5%) of 220 in the R-BEACOPPescalated group died; fatal treatment-related toxic effects occurred in one (<1%) patient in the BEACOPPescalated group and three (1%) in the R-BEACOPPescalated group, all of them due to infection. Interpretation. The addition of rituximab to BEACOPPescalated did not improve the progression-free survival of PET-2 positive patients with advanced stage Hodgkin's lymphoma. However, progression-free survival for PET-2 positive patients was much better than expected, exceeding even the outcome of PET-2-unselected patients in the previous HD15 trial. Thus, PET-2 cannot identify patients at high-risk for treatment failure in the context of the very effective German Hodgkin Study Group standard treatment for advanced stage Hodgkin's lymphoma.