MultipleMyelomaHub

Patients eligible for transplant

Long-term results from the HOVON-50 trial on the use of thalidomide for newly diagnosed multiple myeloma

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The HOVON-50 trial was a randomized, phase III clinical trial designed for newly diagnosed (ND) multiple myeloma (MM), which recruited patients from the Netherlands and Belgium. The experimental arm of the trial included thalidomide, doxorubicin (also known as adriamycin), and dexamethasone (TAd) as an induction treatment, followed by high-dose melphalan, autologous stem cell transplant (ASCT), and thalidomide maintenance. This regimen was compared with the control arm, which consisted of vincristine, doxorubicin, and dexamethasone (VAd), as an induction treatment, and interferon alpha, instead of thalidomide, as a maintenance treatment. After a median follow-up of 52 months, the thalidomide regimen resulted in significantly better event-free survival (EFS) and progression-free survival (PFS) than the control regimen, with no changes in the overall survival (OS).

Niels WCJ van de Donk from the VU University Medical Centre (MC), Amsterdam, the Netherlands, and collaborators, extended the follow-up of the HOVON-50 trial to a median of 129 months. The three survival points that were examined in the prolonged study were EFS, PFS, and OS (annotated as EFSc, PFSc, and OSc, respectively). The results were published in *The Lancet Haematology* in October 2018.

Results are presented as control (VAd induction with interferon alpha maintenance) *versus* (*vs*) thalidomide treatment (TAd induction with thalidomide maintenance).

Study Design:

- Total number of patients: 556 (268 *vs* 268)
- Age range: 18–65
- Durie-Salmon stage: II or III
- WHO performance status: 0–3
- Control group induction: three 28-day cycles of vincristine (0.4 mg by intravenous [IV] infusion on days 1–4), doxorubicin (9 mg/m^2 by IV infusion on days 1–4), dexamethasone (40 mg orally on days 1–4, 9–12, and 17–20)
- Thalidomide group induction: three 28-day cycles of thalidomide (200–400 mg orally on days 1–28), doxorubicin (9 mg/m^2 by IV infusion on days 1–4), dexamethasone (40 mg orally on days 1–4, 9–12, and 17–20); low molecular weight heparin for prophylaxis against thrombosis
- Stem cell mobilization regimen: cyclophosphamide, doxorubicin, and dexamethasone (CAd)
- High-dose melphalan: 200 mg/m^2 IV at 6-8 weeks after stem cell harvest
- Control group maintenance: interferon alpha (3x10^6 international units, subcutaneously, three times per week) starting at 2–3 months after high-dose melphalan

- Thalidomide group maintenance: thalidomide (50 mg, orally, daily) starting at 2–3 months after high-dose melphalan, without venous thromboembolism prophylaxis
- Maintenance treatment was stopped in cases of relapse, progression, or the occurrence of adverse events (AEs); it was also stopped if a second allogeneic stem cell transplant (allo-SCT) followed an ASCT

Key Data:

- Number of patients who received high-dose melphalan and SCT: 219 *vs* 221
- At a median follow-up of 129 months (interquartile range [IQR], 123–136): 125 surviving patients; this does not include the 114 patients who were censored at the time of allo-SCT
- Median duration of maintenance: 11 months (range, 6–24) *vs* 19 months (range, 6–37)
- Median EFSc: 22 months (range, 10–41) *vs* 33 months (range, 14–91) (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.54–0.81, $P < 0.0001$)
- Median PFSc: 23 months (IQR, 11–41) *vs* 34 months (IQR, 17–98) (HR, 0.64; 95% CI, 0.52–0.79, $P < 0.0001$)
- Median OSc: 61 months (IQR, 33–not reached) *vs* 75 months (IQR, 29–not reached) (HR, 0.81; 95% CI, 0.65–1.02, $P = 0.075$)
- During induction, transplant, and maintenance the thalidomide achieved slightly better responses compared with the initial analysis at 52 months follow-up:
  - At least partial response = 211/268 (79%) *vs* 235/268 (88%) patients, $P = 0.006$
  - Complete response = 63/268 (24%) *vs* 87/268 (32%), $P = 0.021$
  - At least very good response = 145/268 (54%) *vs* 180/268 (67%), $P = 0.002$
- Number of patients who stopped maintenance due to treatment-related AEs: 24/90 (27%) *vs* 65/155 (42%); interferon alpha-related events included: 21% psychiatric side-effects, 21% flu-like symptoms, 17% hematological toxicity, 13% skin reactions; thalidomide-related events included: 75% neuropathy, 6% skin reactions
- Second primary malignancies: 23 (observed in 17 patients) *vs* 29 (observed in 24 patients) (HR, 1.08; 95% CI, 0.58–2.03, $P = 0.80$)
- Treatment-related deaths: 19 *vs* 16

Conclusions

The long-term follow-up of the HOVON-50 study revealed significant improvement in EFSc and PFSc in patients treated with thalidomide compared to the control group. These results highlight that MM treatment with thalidomide can still be valuable in countries where there is restricted access to bortezomib and lenalidomide. However, the dose of thalidomide needs to be adjusted accordingly to moderate the severe neuropathy symptoms that many patients experience.

References

van de Donk NW. *et al*. Thalidomide before and after autologous stem cell transplantation in recently diagnosed multiple myeloma (HOVON-50): long-term results from the phase 3, randomised controlled trial. Lancet Haematol. 2018 Oct;5(10):e479-e492. DOI: 10.1016/S2352-3026(18)30149-2.