MultipleMyelomaHub

General MM, Elderly patients, Patients eligible for transplant, Patients non-eligible for transplant

Denosumab *vs* zoledronic acid: phase III study in NDMM patients

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Cancer-induced bone destruction is very common in Multiple Myeloma (MM) patients, such that almost 90% of patients present with detectable bone lesions at diagnosis. Currently, bisphosphonates, such as zoledronic acid (ZA) are the only available treatment for the prevention of skeletal-related events (SREs). Unfortunately, renal impairment is also very common in MM patients, and clinicians need to exercise caution when prescribing bisphosphonates, as these can either induce renal dysfunction or exacerbate pre-existing renal impairment. Therefore, an alternative treatment for MM-related bone disease, with an improved renal adverse event profile, would be beneficial.

Noopur Raje, from the Massachusetts General Hospital Cancer Center, Boston, USA, and colleagues, investigated the efficacy and safety of denosumab in direct comparison with ZA, for the prevention of SREs in Newly Diagnosed Multiple Myeloma (NDMM) patients. The final analysis of this phase III study was published in The Lancet Oncology in February 2018. For details of the study design and data presented at ASCO 2017, see previous MM Hub article.

Key Findings:

Data points are given as denosumab *vs* ZA

- Patients (pts) enrolled = 1718; 859 pts assigned to each treatment group (denosumab or ZA)
- SRE prior to enrolment = 1144 pts; Prior use of bisphosphonates = 37 pts
- Front-line antimyeloma therapy received by >99% of pts
- Median time on study = 17.3 (8.9–28.5) *vs* 6 months (9.4–28.1)
- Median no. of doses received = 16 *vs* 15
- Median creatinine clearance = 77 mL/min; median creatinine = 0.9 mg/dL (same in both groups)
- Pts that remained on treatment through the primary analysis cut-off date = 501 *vs* 499 pts (59%)
- Denosumab was non-inferior to zoledronic acid in delaying time to first SRE (HR = 0.98, 95% CI; 0.85–1.14; *P* = 0.010)
- Median time to first on-study SRE = 22.8 *vs 24.*0 months
- Analysis of time to first and subsequent SRE did not show superiority of denosumab: HR = 1.01, 95% CI, 0.89–1.15; *P* = 0.84; n = 565 for each treatment groups
- Post-hoc landmark analysis at 15 months showed the superiority of denosumab compared to ZA for time to first SRE
- Overall Survival (OS) was similar in both groups: HR = 0.90, (95% CI; 0.70–1.16); *P* = 0.41
- Progression-Free Survival (PFS) = 46.1 *vs 35.*4 months (HR = 0.82; 95% CI; 0.68–0.99; descriptive *P* = 0.036)

Safety:

- Grade 3 Adverse Events (AEs): neutropenia (15% in both groups); thrombocytopenia (14% *vs* 12%); anemia (12% *vs* 10%); febrile neutropenia (11% *vs* 10%); and pneumonia (8% in both groups)
- AEs related to renal toxicity = 10% *vs* 17%
- Study drug discontinuation = 208 pts (13% *vs* 12%)
- Treatment-emergent fatal AEs = 182 patients (10% *vs* 11%); 1 pt in the ZA group had sudden cardiac death
- Osteonecrosis of the jaw:
  - Incidence = 35 *vs* 24 pts (*P* = 0.147)
  - Median time to onset = 17.3 (7.8–20.9) *vs* 13.6 months (8.1–20.3)
  - Resolved for 12 *vs* 6 pts
- Hypocalcemia AEs = 17% *vs* 12%

To conclude, this trial showed that denosumab was non-inferior to ZA in the prevention of SREs, and demonstrated a significantly greater PFS compared to ZA. This finding suggests that denosumab may have an antimyeloma effect in addition to preventing SREs. An improved renal AE profile was observed with denosumab, supporting its use for the treatment of MM-related bone disease in patients with renal compromise. However, the huge differential in cost will be the biggest factor preventing the widespread use of denosumab, so until this can be addressed, many patients are likely to receive ZA as the standard of care (SOC), regardless of renal function.

References

1. Raje N. *et al*. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. The Lancet Oncology. February 2018. DOI: 10.1016/S1470-2045(18)30072-X