MultipleMyelomaHub

Elderly patients

How first-generation novel regimens affect the risk of death in MM

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Autologous stem cell transplantation (ASCT) and the emergence of first-generation novel regimens for combatting multiple myeloma (MM), which include bortezomib (bor), thalidomide (tha), and lenalidomide (len), have significantly increased patient survival during the last decade. Earlier treatment options included traditional chemotherapy agents, which led to high rates of mortality due to drug-related toxic effects.

Sara Bringhen, from the Division of Hematology, University of Turin, Turin, Italy, and collaborators, analyzed collectively data from two clinical trials, GIMEMA MM-03-05 and EMN-01, to understand how first-line treatment with first-generation novel MM drugs affected the mortality of a population of newly-diagnosed (ND) patients with MM, 65 years of age or older. The study was published in Critical Reviews in Oncology/Hematology in September 2018.

Study Design:

- Characteristics of GIMEMA MM-03-05 trial: n = 511 patients; median age = 71 years; induction treatment = bor/melphalan (mel)/prednisone (pre) or bor/mel/pre/tha
- Characteristics of EMN-01 trial: n = 662 patients; median age = 73; induction treatment = len/dexamethasone (dex) or len/mel/pre or len/cyclophosphamide/pre
- Total number of patients examined in this study = 1146/1173 (98%)
- Toxic death = death due to toxicity occurring during first-line therapy or within 60 days since dropout
- Death from other causes = death due to causes other than toxicity occurring during first-line therapy or within 60 days since dropout
- Early death = death (toxic or due to other causes) occurring within 60 days of diagnosis

Key Data:

- Number of patients that suffered toxic death = 47/1146 (4%), of which early deaths = 12/47 (27%)
- Number of patients that suffered death from other causes = 72/1146 (6%), of which early deaths = 7/72 (9%) and death from disease progression = 51/72 (72%)
- Median age of patients who suffered toxic death within ≤ 60 days *vs* > 60 days = 73.5 (interquartile [IQR] range, 72–83.3) *vs* 77 (IQR range, 73–79)
- Median age of patients who suffered deaths from other causes within ≤ 60 days *vs* > 60 days = 78 (IQR range, 70.5–79) *vs* 74 (IQR range, 70–77)
- International Staging System (ISS) III was associated with a high percentage of toxicity-related early deaths, $P = 0.004$

- Causes of toxic death:
  - No effect due to type of treatment: bor-based *vs* len-based treatment combination deaths = 18/503 (4%) patients *vs* 29/643 (5%) patients, *P* = 0.31
  - Cardiac complications = 13/47 patients (28%)
  - Infections = 12/47 patients (26%)
  - Vascular complications = 7/47 patients (15%)
  - Second primary malignancies = 3/47 patients (6%)
  - Bleeding = 4/47 patients (9%)
  - Sudden death = 3/47 patients (6%)
  - Pulmonary events = 2/47 patients (4%)
  - Gastrointestinal events = 2/47 patients (4%)
  - Renal events = 1/47 patients (2%)
- Causes of early toxic death:
  - Cardiac complications = 3/12 patients (12%)
  - Infections = 3/12 patients (12%)
  - Sudden death = 2/12 patients (17%)
  - Second primary malignancies = 1/12 patients (8%)
  - Pulmonary events = 1/12 patients (8%)
  - Gastrointestinal (GI) events = 1/12 patients (8%)
  - Renal events = 1/12 patients (8%)
- Cumulative incidence of toxic deaths = 1.1% at 60 days with an approximate linear increase of 1% every 6 months, reaching 4.1% at 24 months
- Median time to occurrence of death = 8.6 months
- Occurrence of toxic deaths during induction = 77% (93% of cardiac-related deaths, 83% of vascular-related deaths, 67% of infection-related deaths)
- Incidence of toxic deaths per age group: patients < 75 years = 3% (20/773); 75 < patients < 79 = 5% (14/266); patients > 80 years = 13/107 (12%), *P* < 0.001
- Incidence of deaths from other causes per age group: patients < 75 years = 5% (38/773); 75 ≤ patients < 79 years = 9% (24/266); patients > 80 years = 10/107 (9%), *P* = 0.022
- No differences in b_2-microglobulin, albumin, or creatinine levels or the stage of the International Staging System (ISS) were observed between patients > and < 80 years of age
- Grade 3–4 adverse events (AEs):
- Type = infectious, cardiac, vascular, or GI
- Occurrence = 199 patients (17%)

- Development of grade 3–4 AEs increased risk of death (hazard risk [HR], 1.80; 95% confidence interval [CI], 1.4–2.27, *P* < 0.001) and/or risk of disease progression (HR = 1.44; 95% CI, 1.20–1.73, *P* < 0.001)

Conclusions

The present study shows that the use of first-generation anti-MM agents results in a low incidence of toxicity-related deaths in NDMM patients, aged 65 years or older. This may be due to the high therapeutic efficacy and reduced toxicity of new therapies compared to the previously used chemotherapy agents. Patients over the age of 80 are more prone to toxic death, mainly because of increased frailty caused by the disease and other comorbidities. The study underlines the need to adjust MM dosage treatment according to individual characteristics of patients, including their age and physical condition.

References

Bringhen S. *et al.* Early mortality in myeloma patients treated with first-generation novel agents thalidomide, lenalidomide, bortezomib at diagnosis: A pooled analysis. Critical Reviews in Oncology/ Hematology. 2018 Oct; 130:27–35. DOI: 10.1016/j.critrevonc.2018.07.003.