Toxicity Spectrum Recalibration With Daratumumab–Bispecific Combination Therapy in Relapsed/Refractory Multiple Myeloma: A Pooled Comparative Analysis

Adarsh Vardhan Tangella, MBBS, Department of Medicine, MedStar Washington Hospital Center, Washington, DC
Andrew Tiu, MD, Department of Hematology and Oncology, MedStar Washington Hospital Center, Washington, DC

Background

Bispecific antibodies targeting B-cell maturation antigen (BCMA) or GPRC5D have transformed the treatment of relapsed/refractory multiple myeloma (RRMM). As daratumumab–bispecific combinations move earlier in the treatment paradigm, understanding whether CD38-directed therapy alters the toxicity profile of T-cell–redirecting therapy is increasingly important.

We compared inflammatory, infectious, and hematologic toxicities between bispecific antibody monotherapy and daratumumab–bispecific combination regimens.

Methods

We performed a systematic pooled comparative analysis of 5 prospective trials of bispecific antibody therapy in RRMM. Monotherapy cohorts included teclistamab (MajesTEC-1), talquetamab (MonumenTAL-1), and elranatamab (MagnetisMM-3); combination cohorts included talquetamab–daratumumab (TRIMM-2) and teclistamab–daratumumab (MajesTEC-3).

Prespecified outcomes included cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), grade ≥3 infections, and grade ≥3 cytopenias. Frequency-weighted pooled estimates were complemented by Bayesian beta-binomial modeling to estimate absolute and relative differences in toxicity with 95% credible intervals (CrIs).

Results

933
Patients pooled (585 monotherapy, 348 combination)

1.60×
Relative risk of grade ≥3 neutropenia with combination therapy

Any-grade CRS occurred in 71.5% of patients receiving monotherapy versus 63.5% receiving combination therapy, while ICANS occurred in 5.8% versus 1.1%, respectively. Severe CRS remained uncommon in both groups.

In contrast, grade ≥3 infections occurred in 33.7% of patients receiving monotherapy versus 49.4% receiving combination therapy. Bayesian analysis estimated an absolute increase in severe infection risk of 15.7% (95% CrI, 8.8%-22.5%) and a relative risk of 1.47 (95% CrI, 1.28-1.69) with combination therapy.

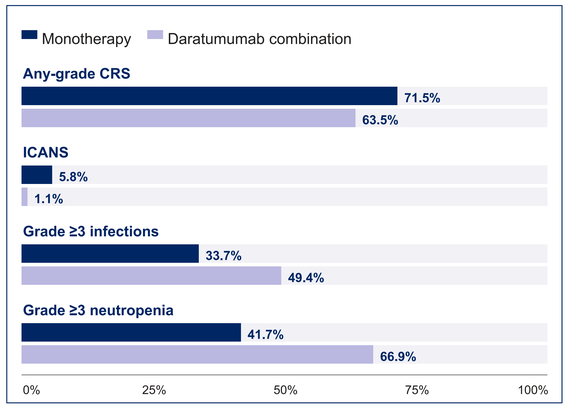
Grade ≥3 neutropenia occurred in 41.7% versus 66.9%, corresponding to an absolute risk increase of 25.2% (95% CrI, 17.9%-32.3%) and a relative risk of 1.60 (95% CrI, 1.43-1.79). MajesTEC-3 additionally demonstrated substantial hypogammaglobulinemia and immunoglobulin replacement requirements.

Included Trials

Table 1. Trials contributing to the pooled analysis

Trial	Regimen	Arm
MajesTEC-1	Teclistamab	Monotherapy
MonumenTAL-1	Talquetamab	Monotherapy
MagnetisMM-3	Elranatamab	Monotherapy
TRIMM-2	Talquetamab–daratumumab	Combination
MajesTEC-3	Teclistamab–daratumumab	Combination

Figure 1. Toxicity by regimen: monotherapy vs. daratumumab combination



Bars show pooled crude incidence for each endpoint by regimen. Scale is 0–100%.

Table 2. Pooled comparative outcomes

Outcome	Mono	Combo
Any-grade CRS	71.5%	**63.5%**
ICANS	5.8%	**1.1%**
Grade ≥3 infections	33.7%	**49.4%**
Grade ≥3 neutropenia	41.7%	**66.9%**

Combination therapy: infection RR 1.47 (95% CrI, 1.28–1.69); neutropenia RR 1.60 (95% CrI, 1.43–1.79).

Conclusions

Daratumumab–bispecific combinations demonstrate a distinct toxicity profile characterized by lower inflammatory toxicity but greater severe infectious and hematologic toxicity compared with bispecific monotherapy.

Rather than uniformly increasing toxicity, addition of CD38-directed therapy may recalibrate the toxicity spectrum from predominantly cytokine-mediated complications toward deeper immunosuppression, supporting intensified infection prevention, immunoglobulin monitoring, and supportive care as these combinations move earlier in RRMM treatment.

References

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