**Review of the following article**

|  |
| --- |
| **Evaluation of Daratumumab for the Treatment of Multiple Myeloma in Patients With High-risk Cytogenic Factors: A Systematic Review and Meta-analysis (JAMA Oncology)** |

A well designed meta-data analysis. Evaluation of Daratumumab for Treatment of Multiple Myeloma (MM) in patient with High-risk Cytogenetic factors.

Background

Daratumumab is a monoclonal antibody that attaches to a protein called CD38 present on the surface of some types of immune cells and cancer cells including myeloma cells. Daratumumab may block CD38 and help the immune system kill cancer cells.

Multiple Myeloma (MM) is a malignant disorder of plasma cells. The disease represents 2% of all malignancies. MM is twice more common in black people than white, slightly more common in males than females, the median age at diagnosis 71 years. The cell origin is probably post-germinal centre B-lymphoid. Oncogene mutations include ras, p53, myc and translocations to 14q occur. Cyclin D1 is often expressed. Chromosome 11 and 13q deletions generally indicate poor prognosis. The meta-analysis discussed here focused on different high-risk cytogenic factors than what was just covered above.

The clinical features include bone pain especially lower back pain and in some cases pathological bone fracture. Bone marrow failure due to marrow infiltration. Infection due to lack of normal immunoglobin production. Renal failure due to hypercalcaemia, infection and deposition of paraprotein uric acid and amyloid.

Standard treatments for;

Over 65’s include melphalan, prednisolone and thalidomide (MPT)

Under 65’s include cyclophosphamide, dexamethasone thalidomide (CDT) followed by high dose Melphalan and autologous stem cell transplant. For patients under 50 allogeneic stem cell transplant may be an option and may prove curative, but complications include graft versus host disease (GVHD), and death.

Most patients relapse and median survival is 4 – 6 years from diagnosis. Relapsed patients can be treated with Idarubicin and dexamethasone. Newer drugs include Lenalidomide and the proteasome inhibitor Bortezomib.

Radiotherapy is useful in localised skeletal disease.

The study centred on the using Daratumumab to backbone (add-on therapy) existing MM regimens and monitor improved progression-free survival (PFS) rates. There were 4 distinct groups;

1. Newly Diagnosed High risk MM (HRMM), where HRMM is defined as having cytogenic abnormalities t (4; 14), t (14; 16) or deletion (17p) is determined by fluorescence in situ hybridization (FISH).
2. Relapsed or refractory HRMM.
3. Newly Diagnosed Standard Risk MM (SRMM), where SRMM is defined as absence of cytogenic abnormalities t (4; 14), t (14; 16) or deletion (17p) as determined by FISH.
4. Relapsed or refractory SRMM.

The search strategy was comprehensive several different medical databases including MEDLINE and EMBASE. The keyword terms applied seemed simple and reasonable search terms to use combining potential disease and drug terms.

Multiple Myeloma OR plasmacytoma and Daratumumab or Darzalex or HuMax CD38.

The search was carried out by two different medical librarians and the results assessed by Cohen’s K (0.85, near perfect agreement) statistic for reproducibility. The search yielded 5193 articles, and eventually 6 randomized phase 3 trials where selected.

The statistical analysis was worthy of note and was conducted in a systematic and comprehensive way in order to eliminate potential sources of bias. After extracting the progression free survival (PFS) hazard ratios (HR) for the four groups, the relative log-HRs using the Der-Simonian Laird random effects model. The Log-HR (parameter estimates) are taken instead of HR to provide symmetrical confidence intervals. The random effects model examines both within study variability, (also achieved through a fixed effects model) and between study variability as a component of variance of the average effect of interest. The random effects model results in larger standard errors and therefore wider confidence intervals.

A sensitivity K-1 analysis was done and an influence plot constructed, to determine if any one study influenced the overall result. A funnel plot was also constructed to assess the presence of publication bias and eliminate only the inclusion of statistically significant results. The influence plot and funnel plot was not provided in this article to view, one can only assume that the results did not yield any surprises! The survival analysis was reported on intention to treat (ITT) and the toxic effects on per-protocol, i.e. patient had treatment exposure.

One particular problem to watch for in this meta-analysis is clinical heterogeneity; differences in patient population outcome measures, definition of variables, duration of follow-up. The authors of this meta-analysis were very careful to categorize the patient groups through presence of absence of cytogenic abnormalities through FISH analysis. There were differences into FISH analysis between the 6 studies.

The biases were addressed pretty well in this meta-analysis. Five of the six trials were deemed of low risk of selection bias. The CANOR trial did not have complete randomization data available for the meta-analysis therefore selection bias could not be determined. All 6 trials where open-label studies therefore no blinding (investigator bias may be a problem), but in this case open-label trials are appropriate because you are comparing two very similar treatment groups to determine which is more effective. There was also no control (placebo) group. There was no blinding of outcome assessment so there was a possibility of detection bias, the detection bias was somewhat mitigated as 3 of the trials had a computer algorithm to evaluate treatment response.

The results of the meta-analysis showed that addition Daratumumab to ‘backbone’ MM chemotherapy regimens resulted in overall improvement of progression free survival for HRMM versus SRMM and in newly diagnosed versus relapsed refractory MM. The level of improvement was greater in the SRMM versus HRMM, and Relapsed / Refractory versus newly diagnosed. The Cochran Q test for homogeneity was non-significant (good) for newly diagnosed and Relapsed HRMM / SRMM and Newly diagnosed SRMM. The Cochran Q test for homogeneity for relapsed SRMM was significant indicating some heterogeneity. The pattern was similar for the index of heterogeneity, the relapsed SRMM group again being the ‘odd one out’.