Panthera R&D Program for Hemato-Oncology

Predictive gene expression-based biomarkers for the treatment of multiple myeloma patients

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Introduction

Despite recent advances in drug development, multiple myeloma (MM) is still considered to be incurable, with most patients relapsing and eventually becoming refractory to therapy. Due to the increasing number of available treatments there is a rising need for treatment selection, especially in the context of the heterogeneous genetic composition underlying myeloma pathogenesis. In this study we aim to find biomarker-informed treatment benefit that could assist patients and their physicians in therapeutic decision making.

Methods

SkylineDx

As part of the Horizon 2020 funded MMpredict project, a total of 862 MM patients with previously bio-banked material were recruited from the EMN-02/HOVON-95 (n=283), HOVON123 (n=121) and HOVON87/NMSG18 (n=180) trials. Moreover, patients were included from the National University Health System (NUHS) Singapore (n=74), the Munich Leukemia Laboratory in Germany (n=37) and the University of Turin (UNITO) in Italy (n=167). For all these MM patients the gene expression-based MMprofilerTM test was performed, providing SKY92 risk classification, as well as the MM clusters (CD1, CD2, CTA, HY, LB, MF, MS, Myeloid, NFKB, NP, PRL3 and PR) biomarker results. Clinical data and patient characteristics - including cytogenetics (t(4; 14), t(11; 14), t(14; 16)/t(14; 20), gain(1q), del(13q) and del(17p)) - were collected from their health records. For the analysis all patients we scored either positive or negative for the drug type(s) they have been exposed to in the treatment-line corresponding with the bone marrow aspirate, respectively Thalidomide-based, Lenalidomide-based, IMiDs, Bortezomibbased, Proteasome inhibitors and DNA alkylating agent based and related to progression-free survival outcomes. Hazard ratios were calculated for the different drug types in the context of each biomarker - both positive and negative. A Cox proportional hazard model and a false discovery rate adjusted Wald two-sided p-value.

Results

This diversely-treated, multicenter cohort consisted mainly of newly diagnosed MM patients (n=818) with a median age of 66 (range: 28-90) and covering all Revised ISS defined risk groups (n=746); I 17%, II 71% and III 12%, respectively. In patients that did not receive a stem cell transplant (n=652), a significantly longer PFS was observed for Bortezomib treated patients positive for the Myeloid cluster (21.6% of cases, HR: 0.51, p=0.022) and for del(13p) (33.3% of cases, HR: 0.64, p=0.046). Moreover, for patients positive for the PR cluster, PFS was significantly longer among patients receiving DNA alkylating agents (12.8% of cases, HR: 0.38, p=0.028).

Conclusion

We have discovered novel, predictive biomarkers that potentially could help individual MM patients and their physicians in choosing the best personalized treatment strategies.

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