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ORAL ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Bone Marrow Immune Signatures in Multiple Myeloma Are Linked to Tumor Heterogeneity and Treatment Outcome

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Abstract In multiple myeloma (MM), malignant plasma cells interact with a bone marrow microenvironment (BME) that promotes disease progression and drug resistance. Anti-CD38 monoclonal antibodies increase efficacy when added to standard-of-care (SOC) regimens as reflected by minimal residual disease-negativity (MRD-neg) rates of >50 % after induction therapy in newly diagnosed MM (NDMM) patients treated with SOC plus isatuximab within the GMMG-HD7 trial (Goldschmidt et al. Blood (2021)). Here, we have characterized longitudinally collected BME samples (n = 1,225) to (i) associate the BME composition with MM cytogenetic and molecular subgroups, (ii) understand the influence of treatment combinations involving isatuximab on the BME and (iii) link BME alterations to therapy response including MRD-neg and progressive disease.

NDMM patients were treated with lenalidomide/bortezomib/dexamethasone (RVd) alone or in combination with isatuximab (isa-RVd, NCT03617731). By combining high-dimensional flow cytometry (using 38 surface markers) and single cell RNA-sequencing with an additional capture of surface markers (CITE-seq with 192 surface markers, in a subset of patients) we characterized cellular and molecular changes of the BME at baseline (n = 469), at the end of induction therapy (n = 391) and after autologous stem cell transplantation (ASCT) (n = 365). Patients were defined as MRD-neg when both assessments of MRD, by flow (EuroFlow) and next-generation sequencing (ClonoSEQ) were negative according to standard protocols. Paired flow cytometry samples and CITE-seq data were integrated with a variational autoencoder to create a BME reference atlas. This allowed us to map cell state specific transcriptional signatures from scRNA-seq onto the flow cytometry data. Compositional subgroups within the BME at baseline were revealed by principal component analysis and clustered. Cytogenetic aberrations, assessed by iFISH, and mutations, called using WGS, were linked with BME cell type abundance using generalized linear models.

We generated a comprehensive BME dataset for MM that comprises >120 million single cells. Based on distinct compositional signatures of the BME, we were able to define at least 6 subgroups at baseline as well as treatment-specific changes of the BME. The size of our patient cohort (n = 469) enabled us to assess combinatorial genetic aberrations associated with complex patterns of compositional changes. For example, hyperdiploid patients with a 1q-gain (+1q) displayed a significant depletion of B cell lineage cell types, whereas patients with +1q and a t(4;14) translocation displayed a significantly increased abundance of the monocyte compartment, linking tumor heterogeneity to immune alterations in the BME. In addition, we also found changes in the BME that were associated with mutations in MM driver genes, including a compromised CD4+ memory compartment in NRAS-mutated patients. Treatment-induced changes involved major effects of isa-RVd induction on CD38+ non-tumor cell types such as a significant depletion of NK cells. In contrast, the T cell abundance remained stable. Interestingly, the use of isa-RVd also conferred a significant impact on the BME composition after ASCT, pointing towards an effect of isa on the regeneration of the BME post-transplant. Finally, we linked MRD status after induction therapy and relapse risk to BME composition. In patients with isa-RVd treatment (n = 239), but not RVd-alone (n = 229), MRD-negativity after induction therapy was associated with a specific BME composition at baseline that was characterized by a significant depletion of CD8+ T cells. While the trial is ongoing, some patients relapsed within two years after start of therapy and showed specific immunological signatures throughout treatment-timepoints. For example, the BME at diagnosis and after ASCT was characterized by a significant depletion of progenitor and stem-cell populations as well as early CD8+ memory cells indicating a predictive immune signature of patients at high risk for early relapse.

BME signatures at baseline and during treatment as defined by our reference atlas enable risk stratifications of MM patients and can identify patients at high risk for early relapse. Longitudinal monitoring of the BME can support clinical decision making, as a compromised CD8+ memory compartment in patients may impact on the efficacy of novel immunotherapies.

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