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ORAL ABSTRACTS

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

Low Levels of Circulating Tumor Cells Correlate with Favorable Clinical Outcome and Unique Biological Features in Newly Diagnosed Multiple Myeloma Patients

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Introduction

Circulating tumor cells (CTCs) have been proposed as a prognostic biomarker in newly-diagnosed MM (NDMM) but their low frequency questions their use in clinical practice. Lower CTC levels (cut-off <0.01-0.07%) correlate with a favorable prognostic outcomes in transplant-eligible (TE) patients (pts); however, several issues remain to be addressed. On clinical grounds, it remains unclear whether there is a similar prognostic cut-off value for transplant-ineligible (TI) pts. Furthermore, it is not clear whether the CTCs mimic the characteristics of a single (main)-site bone marrow (BM) myeloma cells or if they represent the total disease burden, i.e. in cases with extramedullary or macrofocal disease. Moreover, there is limited information of the biological factors that may lead myeloma cells to egress their primary BM site.

Methods

BM and matched peripheral blood (PB) samples from 550 NDMM pts (210 TE, 340 TI) were evaluated with NGF (median LOD $2.1x10^{-6}$) for the presence of myeloma cells. Various multivariable regression models including CTCs, R-ISS, cytogenetic status and LDH were assessed to define the optimal clinical CTC cut-off. The BM niche profiling was examined with mass cytometry (CyTOF, n=15 pts, 8 with no CTCs, 7 with CTCs higher than the cut-off) and various multicolor flow cytometry panels (n=199 pts including 56 pts with no CTCs) that allowed the detection of 32 distinct immune populations.

Results

The median value of CTCs was 0.01% of total PB cells (range: 0.0002%-63%) and in 57/550 (10.4%) pts CTCs could not be detected. Increased levels of CTCs correlated with ISS III stage (median: 0.037%, 0.007% and 0.002% for pts with ISS-3, ISS-2 and ISS-1, respectively; $p<0.0001$), high risk cytogenetics (median: 0.038% vs. 0.006% in standard risk, $p<0.0001$), and higher levels of b2-microglobulin and BM infiltration. Median follow-up was 41 months (range: 5-66 months). PFS and OS were gradually worsened towards a CTCs log increment, independently of ISS, cytogenetic status and LDH. Hence, pts with undetectable CTCs had the most favorable prognosis with a 5-year PFS and OS of 83% and 97% respectively. The optimal clinical CTCs cut-off that stratified pts into two distinct prognostic groups was defined at the level of 0.02%, which was common for both TE (median PFS: NR in both high and low CTC subsets; $p<0.01$) and TI subgroups (median PFS: 47 for low vs. 23 months for high CTCs subset, $p<0.0001$). Importantly, this cut-off, together with the phenotypic classification of pts (MGUS-like, MM-like etc.) could be incorporated in the established R-ISS system, providing an improved ptnts' stratification. The 2-year achievement of MRD negativity was 45%, 67% and 73% for pts with high, low and undetectable CTCs and median time for MRD negativity was 34, 17 and 12 months, respectively ($p<0.001$). Of note, pts with high CTCs who achieved MRD negativity, modulated their unfavorable risk status and showed similar PFS with those who had low CTCs.

In 73/493 (14.8%) pts with detectable CTCs, there was an obvious phenotypic inconsistency between BM myeloma cells and CTCs, either in regard to the relative ratio of the detected (sub)clones, or the appearance of ≥1 phenotypically distinct clonal populations, which were present only in BM or PB. Pts with phenotypic inconsistencies had higher CTC levels and more often diffuse MRI patterns than those with a phenotypic agreement (frequency: 40% vs. 10%; $p<0.01$). To better understand the heterogeneous dissemination of myeloma cells to PB, we compared the BM niche profiles of pts with high CTC levels (>10

$^{-3}$) and those with no CTCs. The analyses highlighted clear differences in the BM composition of the two groups with the BM of pts with no CTCs showing significantly lower levels of T cells, NK cells, TAMs and an increased naïve/memory B cell ratio. Of note, no differences were observed in the prevalence of immunosuppressive cell subsets (Tregs, MDSCs) between the two groups.

Discussion

The presence of CTCs at levels >0.02% confers an adverse prognostic factor for NDMM pts, irrespective of their transplant status. On the contrary, pts with no CTCs have the more favorable outcome and share unique microenvironmental features, which may eliminate CTCs dissemination. Since the liquid biopsy seems to be a better representative of the entire tumor load than a single tissue biopsy, the CTC analysis serves as the new hallmark for the real-time evaluation of a patient's disease and immune status.

Disclosures Migkou: *Janssen-Cilag:* Honoraria; *Glaxo Smith Klein:* Honoraria; *Integris Pharma:* Honoraria. **Gavriatopoulou:** *Celgene/Genesis:* Honoraria; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Takeda:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *GSK:* Honoraria; *X4 Pharmaceuticals:* Research Funding; *Karyopharm:* Honoraria, Research Funding; *Sanofi:* Honoraria. **Kastritis:** *Janssen:* Honoraria, Research Funding; *GSK:* Honoraria, Research Funding; *Pfizer:* Honoraria, Research Funding; *Sanofi:* Honoraria. **Terpos:** *Menarini/Stemline:* Honoraria; *EUSA Pharma:* Honoraria, Other: Travel expenses; *Takeda:* Honoraria, Other: Travel expenses, Research Funding; *Sanofi:* Honoraria, Other: Travel expenses, Research Funding; *Pfizer:* Honoraria; *Amgen:* Honoraria, Other: Travel Expenses, Research Funding; *AstraZeneca:* Honoraria, Other: Travel Expenses; *Janssen:* Honoraria, Research Funding; *BMS:* Honoraria; *GSK:* Honoraria, Research Funding.

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