Myeloid-derived suppressor cells (MDSCs) in metastatic castration-resistant prostate cancer (CRPC) patients

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Background

As hormone-sensitive prostate cancer (PCa) in time evolves into lethal CRPC state it acquires the ability to manipulate the immune system to avoid immune destruction and create a tumour promoting inflammatory and immunosuppressive environment. We investigated peripheral blood and intratumoral immune contexture in relation to systemic inflammation (neutrophil-to-lymphocyte ratio), treatment resistance and patient outcome.

Methods

We prospectively immunophenotyped peripheral blood immune cells of 14 healthy volunteers and of 74 patients that included B-cells, T-cell populations, natural killer cells (NK), polymorphonuclear-MDSC (PMN-MDSC) and monocytic-MDSC (M-MDSC). Phenotypic analyses of immune cell populations were performed with fluorescently labelled antibodies to HLA-DR, CD45, CD15, CD33, CD14 and CD11b, CD3, CD4, CD8, CD19, CD20 and CD56. PMN-MDSCs were defined as $CD15^{+}HLA\text{-}DR^{low}CD14^{-/+}$ and M-MDSCs as $HLA\text{-}DR^{low}CD14^{+}CD15^{-}$ $CD11b^{+}CD33^{+}$. Data were acquired with a BD Canto II with FACS-Diva and analyzed using FloJo Software version 10.0.7. PTEN, Rb1 and Myc status (8q gain) was assessed with targeted amplicon-based sequencing (IonTorrent) of cfDNA (CNVkit V0.3.5). From selected patients CRPC tissue was obtained from metastases within bone (bone marrow trephine), lymph node, or viscera (needle biopsies) for multiplex immunofluorescence imaging of MDSCs (Vectra using InForm v.2.0 Software). We evaluated associations between immune populations and common genomic aberrations, PSA>50% response, PSA-progression-free survival (PSA-PFS) and overall survival (OS).

Results

In the peripheral blood, CRPC patients have decreased B-cells (p=0.003), CD4+ and CD8+ T-cells (both p<0.001) and NK cells (p=0.003) and increased levels of PMN-MDSCs and M-MDSCs (both p=0.001). There were inverse correlations between M-MDSC and NK levels (-0.583, p<0.001) as well as B-lymphocytes (-0.565, p<0.001) and T-lymphocytes (-0.607, p<0.001). M-MDSC counts associated with a shorter PSA-PFS (HR 1.072 with 95%CI 1.001-1.149, p=0.047), while PMN-MDSC associated with a lower likelihood of PSA response (OR 0.310 with 95%CI 0.101-0.954, p=0.001). Four subsets of immune cells associated with OS; NK and CD4+ T-cells associated with a longer OS (HR 0.580 with 95%CI 0.366-0.917, p=0.02 and HR 0.962 with 95%CI of 0.932-0.993, p=0.015, respectively), while M-MDSC and $CD14^{+}CD15^{+}$ PMN-MDSC associated with shorter OS (HR 1.064 with 95%CI 1.021-1.109, p=0.003 and HR 1.13 with 95%CI 1.018-1.247, p=0.021, respectively). Increased PMN-MDSCs and M-MDSC were found in Myc-amplified PCa (20 /57 evaluable with p=0.004 and 19 /55 with p=0.027, respectively), and increased PMN-MDSC levels in cancers with RB1 loss (n=13 /56; P=0.017). In patients with increased levels of systemic inflammation (neutrophil-lymphocyte ratio>3) higher levels of circulating MDSCs (p<0.001) as well as higher tumour-infiltrating MDSCs (p=0.046, n=18) were detected.

Conclusions

Overall, these studies suggest that the peripheral blood immune contexture is hijacked with an immunosuppressed phenotype promoting tumour progression. Therapeutic strategies targeting MDSCs may reverse this immunosuppression, counter treatment resistance and improve outcome of patients with CRPC.

Conflicts of Interest Statement
None

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