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Short communication

Ovarian cancer and the immune system

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ABSTRACT

Short communication in response to the review of Turner et al. entitled "Ovarian cancer and the immune system - the role of targeted therapies" published in Gynecological Oncology. We believe systemic immune parameters might be a good alternative to tumor biopsy to gain insight in the immunological background of ovarian cancer.

With great interest, we read the review of Turner et al. entitled "Ovarian cancer and the immune system – the role of targeted therapies" published in Gynecological Oncology (Turner et al., 2016). The authors intelligibly describe the complexity of the immune system in cancer in a clinically relevant manner. Novel information concerning the immune system in cancer is constantly emerging. Currently, there are several immunotherapy trials, recruiting ovarian cancer patients (Kandalaft et al., 2013). However, selecting the patients who might have the most chance of having a beneficial effect of immunotherapy is difficult.

To date, immunological research has mainly focused on phenotyping the intra-tumoral immune system, while changes in the peripheral immune system have been less investigated. However, the majority of patients with ovarian cancer are diagnosed with advanced disease and 80% of patients will die. The primary tumor site is usually not the cause of death. Therefore, peripheral immune cells possibly reflect the systemic immunosuppressive state better than a tumor biopsy.

Erfani et al. performed a prospective case control study on 17 ovarian cancer patients and 20 age-matched healthy controls (Erfani et al., 2014). They found 2.8% CD4+ CD25+ FoxP3+ regulatory T cells (Treg) in the control group, compared to 5.7% Treg in the patient group ($p = 0.002$) (Erfani et al., 2014). This finding was confirmed by Napoletano et al. on a subset of 25 primary ovarian cancer patients (Napoletano et al., 2010). In this study, newly diagnosed patients with ovarian cancer had $1.5 \pm 1\%$ Treg versus $0.3 \pm 0.1\%$ in the control group ($p < 0.0005$) (Napoletano et al., 2010). In addition to this, Lukesova et al. have determined the phenotype of peripheral leukocytes and ascites associated leukocytes in ovarian cancer (Lukesova et al., 2015). In 53 ovarian cancer patients a broad T cell and natural killer cell (NK) staining panel was performed on ascites and peripheral blood: CD4, CD3, CD69, CD8, CD57, CD25, CD14, CD45RO, CD45RA, HLA-DR, TCRαβ, TCRγδ, CD56, NKG2D, CD19 and CD16. In this study, relative numbers of NK cells, natural killer T cells (NKT), cytotoxic T cells (Tc) and T helper cell (Th) subtypes in ascites correlated with overall survival. T cell and NK cell counts in peripheral blood were correlated to the numbers in ascites, but not to survival (Lukesova et al., 2015). Auer et al. investigated the correlation between the pattern of peritoneal spread of the tumor (milliary vs non-milliary) and immune parameters. In a series of 30 patients with high-grade serous ovarian cancer, no differences in T, Th, Tc, Treg, NK, NKT or B cell was observed in peripheral blood, between both patterns of peritoneal spread. In this study no correlation of immune cells with overall or progression free-survival was mentioned (Auer et al., 2016).

The systemic presence of immunosuppression in serum was investigated by our research group. Studying the serum samples of 80 women with ovarian cancer, we observed that CCL-2 (chemokine (C-C) ligand-2), produced by immunosuppressive tumor associated macrophages (TAM) and Galectin-1 had a negative effect on prognosis of ovarian cancer patients (Coosemans et al., 2016). Galectin-1 is a natural immunosuppressive molecule that will reduce T cell responses (Rabinovich and Ilarregui, 2009).

Although information on the systemic status of the immune system is very scarce, all results point to a highly immunosuppressive environment. This is a major factor compromising the success rate of anticancer immunotherapy. The currently available chemotherapies can influence

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this immunosuppressive state. The team of Sjoerd van der Burg recently demonstrated that synergy of Paclitaxel-Carboplatin and peptide vaccination coincided with a decrease in circulating and intratumoral (immunosuppressive) myeloid cells in cervical cancer (Welters et al., 2016). Furthermore, it is known from studies in pancreatic cancer and non-small cell lung cancer that Gemcitabine decreases circulating Treg and increases $CD11c^{+}$ dendritic cells and $CD14^{+}$ monocytes in peripheral blood (Galluzzi et al., 2015).

To conclude, we would like to stress the importance of the immune system in ovarian cancer but we also want to advocate the importance of the status of the peripheral immune system. Ovarian cancer is a widespread disease, influencing the whole body. Therefore we should look into peripheral leukocytes and cytokines as a diagnostic, prognostic or therapeutic predicting biomarker for ovarian cancer. At the same time, we should also investigate the evolution of these cells in response to treatment and relapse.

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