



# Crucial role of vascular endothelial growth factor in the immune system of patients with ovarian cancer

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Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that targets vascular endothelial growth factor A (VEGF-A) (1). Since the 2000s, several large phase III clinical trials, such as GOG218 and ICON7, have shown that bevacizumab has a drastic effect on ovarian cancer prognosis, in combination with standard chemotherapy (2,3). In patients who showed platinum-sensitive relapse, bevacizumab has also been shown to improve progression-free survival (PFS) (OCEANS) (4), although no overall survival (OS) benefit was found. Furthermore, in platinum-resistant relapse, a recent phase III trial (AURELIA) reported an increase in response rate and a doubling of PFS (6.7 *vs.* 3.4 months) in patients who received a single agent chemotherapy plus bevacizumab, compared to those who received chemotherapy alone (5). These clinical results show that angiogenesis via VEGF signaling is a crucial contributor to ovarian carcinogenesis and progression. Consequently, bevacizumab has great potential for ovarian cancer treatment. Indeed, it is well known that patients with high VEGF expression have significantly poorer survival rates than those with low VEGF expression (6), and that massive ascites contain aberrant high concentrations of VEGF with peritoneal dissemination in advanced or recurrent ovarian cancer (7). The clinical efficacy of bevacizumab is primarily due to its anti-angiogenic effects; however, recent reports have revealed that it has not only direct antitumor effects but also immunomodulatory effects (8).

Recently, Tiper *et al.* reported that conditioned medium from ovarian cancer cell lines and ascites fluid from ovarian cancer patients inhibit CD1d-mediated natural killer T (NKT) cell activation, indicating that ovarian cancer cells

can act as antigen-presenting cells to NKT cells (9). They showed that VEGF modulates ganglioside GD3 expression in ovarian cancer cells, and that ovarian cancer-associated GD3 is responsible for suppressing CD1d-mediated NKT activation. Thus, the blockade of VEGF with bevacizumab or genistein restored NKT cell function, suggesting a novel mechanism by which angiogenic signaling pathways contribute to immune suppression through the alteration of the lipid repertoire, with VEGF serving as one of the modulators (9).

There have been compelling reports that VEGF plays an immunosuppressive role. The most commonly described immune effects of VEGF are those related to dendritic cell (DC) maturation and function. DCs are antigen-presenting cells and are essential for activating a T-lymphocyte response (10). VEGF not only inhibits the maturation of DCs but also impairs the antigen-presenting function of mature DCs (8). Furthermore, immature DCs contribute to ovarian cancer progression by acquiring a pro-angiogenic phenotype in response to VEGF (11). Huarte *et al.* showed that the elimination of pro-angiogenic DCs in a xenograft mouse model significantly delayed cancer growth, resulted in tumor necrosis, and enhanced the effect of cytotoxic chemotherapies (12). Bevacizumab was shown to enhance DC maturation and numbers in peripheral blood from patients with lung, breast, and colorectal carcinoma (13). Therefore, blocking VEGF signaling might be one approach to improve DC responses, hence improving host immune system function and increasing the efficacy of antitumor immunotherapy in cancer patients (8).

Regarding T-cells, ovarian cancer ascites-derived T-cells

secrete VEGF and express vascular endothelial cell growth factor receptor 2 (VEGFR-2) on their surface in response to their activation. VEGF directly suppresses T-cell activation, proliferation, and cytotoxic activity via VEGFR-2, thus suggesting an immunosuppressive effect (14). Consequently, blocking VEGF signaling affects not only angiogenesis but also tumor escape from immune surveillance. Zhang *et al.* revealed that VEGF contributes to vascular remodeling in human arteries through a direct effect on human T-cells that enhances their recruitment to the vessel (15). Bevacizumab inhibited lymphocyte recruitment and ameliorated immune-mediated vascular remodeling, suggesting the possibility of novel therapeutic approaches.

Abundant macrophages exist in massive ascites in advanced ovarian cancer patients. Isobe *et al.* revealed that CD11b+CD14+CD206+ cells, which are predominantly M2-polarized macrophages, are the major source of interleukin-6 (IL-6) (16). Many ovarian cancer cell lines overexpress the IL-6 receptor (IL-6R), suggesting that IL-6/IL-6R signaling acts in a paracrine manner in certain types of ovarian cancer. VEGF induces migration and adhesion of macrophages, and the blockade of VEGF signaling in breast cancer xenografts reduced tumor-associated macrophage (TAM) infiltration (17), which could have significant implications for the clinical use of current and future anti-VEGF therapies.

Recent breakthroughs in clinical trials of therapies designed to modulate immune-mediated killing of tumors have led to increased optimism and a focus on immunotherapy for cancer. Promising therapeutic effects in some solid cancer patients have been reported with the use of anti-programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte-associated 4 (CTLA-4) therapy. An anti-PD-1 antibody, nivolumab, has produced objective responses in approximately 20–25% of patients with non-small cell lung cancer, melanoma, or renal-cell cancer (18). In patients with platinum-resistant ovarian cancer, nivolumab demonstrated encouraging clinical efficacy and tolerability (19). The disease control rate in all 20 patients was 45%. The median PFS was 3.5 months and the median OS was 20 months. Peng *et al.* reported that chemotherapy with paclitaxel induces local immunosuppression in ovarian cancer through NF- $\kappa$ B-mediated PD-L1 upregulation (20). Therefore, a combination of cytotoxic chemotherapy and immunotherapy targeting PD-1/PD-L1 signaling may improve the antitumor response for refractory ovarian cancers. Ipilimumab, an anti-CTLA-4 antibody, potentiates

an antitumor T-cell response. Ipilimumab improved OS in patients with previously treated metastatic melanoma in a phase III clinical trial (21). Such therapies targeting immune checkpoints might be a breakthrough to improve the prognoses of ovarian cancer patients.

Collectively, available data suggest that blocking VEGF signaling targets not only angiogenesis but also tumor escape from immune surveillance. Given that immunotherapy is promising and clinically feasible in ovarian cancer treatment, the extent of the effect of VEGF on the immune system may be used to select patients likely to benefit from anti-angiogenic therapies.

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