Tumor-infiltrating lymphocytes influence on prognosis and outcome of ovarian cancer

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Abstract

Ovarian cancer has the highest case fatality rate among the gynecological malignancies. Most cases of ovarian cancer are diagnosed at an advanced stage. Although more than half of patients are in remission following the “debulking” surgery and first-line platinum-based chemotherapy, the five-year survival rate remains less than 25%. In case of treatment on the early stages, the 5-year survival rate reaches 90%. No precise prognostic biomarkers for ovarian cancer have been available until the present. At the same time, growing evidence suggests that ovarian cancer is an immunogenic disease that can be identified by the patient’s (host) immune system. The interaction between the host immune system and cancer cells is crucial for tumor progression. In recent years, many studies have been devoted to the study of tumor-infiltrating lymphocytes (TILs) in cases of ovarian cancer. The presence of tumor-infiltrating T-cells in ovarian cancer is a clear prognostic indicator and correlates with improved clinical outcomes. It is thought that the presence of tumor-infiltrating CD8+ T cells is associated with improved survival in almost all solid tumor types. Favorable clinical outcome and reliable prognosis, following the “debulking” surgery and adjuvant chemotherapy is in close correlation with the existence of TILs not only in the cancer tissue, but also in its microenvironment. (TCM-GMJ April 2020; 5(1):P36-P39)

Keywords: Ovarian cancer; Tumor-infiltrating T-cells; “Debulking” surgery; Chemotherapy.

O varian cancer has the highest case fatality rate among the gynecological malignancies(1). Most cases of ovarian cancer are diagnosed at an advanced stage. Although more than half of patients are in remission following the “Debulking” surgery and first-line platinum-based chemotherapy, the five-year survival rate remains less than 25%(2,3). In case of treatment on the early stages, the 5-year survival rate reaches 90%. The tumor stage, existence of the residual tumor tissue After "Debulking" surgery and chemosensitivity have a significant impact on the outcome of ovarian cancer (4,5). As far as the tumor becomes resistant to chemotherapy, the disease recurs in 2-5 years(6-8). Thus, predicting the outcome of the treatment of ovarian cancer, as well as determining a progression-free and survival period is difficult (9).

No precise prognostic biomarkers for ovarian cancer have been available until the present. At the same time, growing evidence suggests that ovarian cancer is an immunogenic disease that can be identified by the patient’s (host) immune system(11). The interaction between the host immune system and cancer cells is crucial for tumor progression. In recent years, many studies have been devoted to investigating cases of ovarian cancer (12,13). TILs are WBC, which include T cells, B cells, macrophages or natural killer cells, and are localized in the parenchyma and stroma of the tumor. These cells recognize tumor cells and give an immune response. The first report on the importance of TIL in case of ovarian cancer and its association with the survival was presented by Ma in 1991(14).

Further studies also confirm that the presence of tumor-infiltrating T-cells in ovarian cancer is a clear prognostic indicator and correlate with improved clinical outcomes(11,15). However, some studies have indicated the need for further study/confirmation of the prognostic value of these lymphocytes(16-18).

Today, among all TIL subtypes, CD8 + T cells are considered to be the most important component with antitumor activity(19-22). CD8+ T-cells perform "clearance" of the tumour through several mechanisms: a) They can detect specific antigen, which is located on the surface of the tumor, release cytotoxic molecular granzyme B and perforin. Perforin produces the hole in the tumor cell membrane, whereas granzyme B enters into cell by perforin and activates special enzymes – caspases which leads to process of apoptosis; b) Can induce tumor cell death through Fas-Fas ligand interaction. The said transmembrane protein (type II) represents tumor necrotizing factor family, which acts as the receptor, located on the T-cell and ligand, located on the tumor cell. T-lymphocyte, activated by the mentioned receptor-ligand interaction causes apoptosis in the tumor cell and leads to its death; c) CD8+ Cytokines released by T-cells, for example, IFNγ and TNFα, may have antitumor effect

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by induction of "senescence" of cancer cells.

It is thought that the presence of tumor-infiltrating CD8 + T cells is associated with improved survival in almost all solid tumor types(23).

CD8 + T-cells are stimulated by peptides, coming from the degradation resulted of proteins, bound with HLA class I molecules(24). CD8 + T-cells destroy tumor cells, resulting in the production and release of anti-inflammatory cytokines that promote the elimination of perifocal inflammatory processes. Therefore, The existence of CD8 + TILs in the epithelial component of ovarian cancer indicates a good prognosis(20,25-30).

Favorable clinical outcome and reliable prognosis, following the “Debulking” surgery and adjuvant chemotherapy is in close correlation with the existence of TILs not only in the cancer tissue, but also in its microenvironment(11,13).

In order to determine the prognostic significance of TIL in case of ovarian cancer, meta-analyses of published literature was conducted, aiming at evaluating the impact of TIL status on survival rate(28). It has been revealed that only high concentrations of CD3 +, CD8 +, or CD103 + TILs are indicating improved survival, while, only FoxP3 + TIL, and/or CD8 +/FoxP3 + and CD8 +/ CD4 + ratios do not correlate with prognosis. In the case of ovarian cancer, the major determinants of the prognostic significance of TIL are the location, subtype, and concentration of TIL together. Some studies have shown that the location of TIL in tumor tissue is crucial for determining ovarian cancer prognosis(20,26).

Anti-tumor immune reactions involving reactive T cells and tumor-specific antibodies can be detected in peripheral blood, tissues of the ovarian cancer and ascites fluid (31-34). In addition, it has been revealed that despite the presence of reactive CD8 + T cells, tumor progression can still occur: Cancer cells can create an immunosuppressive microenvironment by releasing inhibitory cytokines, expressing inhibitory molecules as well as immunosuppressive cells in order to restrain anti-tumor activity of CD8+ T (“Downstream Regulation”)(35).

The process and outcome of leukocyte infiltration into tumor tissue are being actively investigated in case of tumors with the various proliferative potential. For example, it has been revealed that even with rapidly spreading breast cancer, tumor tissue infiltration with CD8 + T cells is associated with a better outcome(36-37).

The lymphocytes, infiltrated in tumor tissue (4,38,39) reveal oligoclonal expansion(40,41), recognize tumor antigens(38,42-44) and have a tumor-specific cytolytic effect in the cell(45) even in case of ovarian cancer.

Interferon-γ and interleukin-2, which are released by T-cells upon activation of antigens(46), cannot be identified in most tumors that do not contain T-cell islets, but is easily detected in the tumors, in the tissues of which T-cells were detected in the form of islets. Numerous studies have shown that despite the different mechanisms by which tumors can evade immune surveillance(47-51), it has been confirmed that immune systems actively attacks ovarian cancer in one part of patients(38-45).

Based on the aforesaid, the role of immune status in the human body and its impact on tumor processes is underlined. Quantitative and qualitative analysis of TIL subtypes (killers, helpers, suppressors), taking into account the specificity of topography (distribution within the tissue of the ovarian cancer), has the potential to become not only one of the prognostic markers of ovarian cancer, but also to form the basis for new therapeutic approaches.

References


