

Blockade of Interleukin-6 Signaling Reduces Immunosuppressive Regulatory T Cells in Ascites of Advanced Epithelial Ovarian Cancer and Improves Chemotherapy Efficacy

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ABSTRACT

Background and Aims: Recurrent epithelial ovarian cancer is often associated with ascites which is resistant to chemotherapy. Malignant ascites may also aid tumour persistence by harbouring immunosuppressive regulatory T cells (Tregs) that render effector T cells (Teff) dysfunctional, as well as inflammatory soluble factors such as interleukin 6 (IL-6). Upregulation of Tregs and IL-6 have been correlated separately with tumour progression and reduced survival in advanced EOC, however their relationship is not well understood. We studied the immunomodulatory effect of IL-6 on Tregs within malignant ascites in-vitro. **Methods:** Peripheral blood mononuclear cells (PBMC) from healthy donors were incubated with media or cell-free ascites from advanced EOC patients for 48 hours. Exogenous IL-6 was used at 50ng/ml to mimic the natural level in ascites. Bioactive IL-6 within the ascites was neutralized with human monoclonal antibody to IL-6, alone or in combination with chemotherapy drug. The frequency and phenotype of Tregs as well as Teff were evaluated. **Results:** We show for the first time that blockade of IL-6 activity in ascites decreases the frequency of Treg, otherwise induced by exogenous IL-6 in media and ascites, and increases the ratio of Teff/Tregs and improves responsiveness to taxane efficacy. **Conclusions:** Antibody blockade of IL-6 specifically within ascites may offer a novel, clinically translatable strategy to increase immune-competence in the local tumour microenvironment, and combined with chemotherapy, may make cytotoxic chemotherapy more effective in advanced/recurrent EOC.

Evaluation of Systematic Pelvic Lymphadenectomy in Endometrioid Adenocarcinoma with Grade 1

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ABSTRACT

Background: The surgical management of early stage of endometrial carcinoma is still debatable despite the recommendation of systematic lymphadenectomy with total hysterectomy and bilateral salpingo-oophorectomy (SLTH-BSO) by the FIGO. This is due to the lack of supporting evidence on the significant improvement of patients' survival years. Considering that suboptimal surgical intervention for these patients may lead to potential short and long term sequelae, it is important to investigate the clinical value of this treatment especially in grade 1 disease. **Aims:** To evaluate the efficacy of SLTH-BSO in determining lymph node involvements in grade 1 Endometrioid adenocarcinoma. **Methodology:** A cross sectional study was conducted in two Gynae - Oncology units in Klang Valley from 2014-2017. All patients with preoperative diagnosis of endometrial carcinoma were recruited and underwent total hysterectomy with systematic lymphadenectomy and bilateral salpingo-oophorectomy by two gynae-oncology surgeons. Data mining from 196 patients was performed on patient's profile (age, race, parity, comorbidity i.e. diabetes mellitus) and histopathology examination (HPE) findings of surgical specimen (type of cancer, histology grading, myoinvasion involvement and lympho-vascular invasion). Statistical analysis was done using IBM SPSS version 22. Descriptive test was used to analyse the demographic data whilst multiple logistic regression test for the correlation between systematic pelvic lymphadenectomy and the various histopathological factors. Two-sided of $p < 0.05$ was considered as statistically significant result **Results:** Complete data was successfully extracted from 150 patients. Median age was 54 (range: 27-80) and 14% was below 40 years. HPE findings from the specimens showed endometrioid adenocarcinoma as the commonest type (83.3%, n=125). From this, 29.8% (n=37) has G1 disease, 56.8% G2 and 13.4% has G3. All patients with G1 disease of this type regardless of the involvement of LVSI or myoinvasion, were found to have negative lymph node. 91.8% (n=34) has myoinvasion < 50% and 83.7% (n=3) has negative LVSI. Two patients were not documented of the LVSI involvement. **Conclusion:** We showed that total hysterectomy and bilateral salpingo-oophorectomy without lymphadenectomy is an acceptable practice for G1 disease in Endometrioid adenocarcinoma however further study needed to get larger sample size to confirm if myoinvasion > 50% or LVSI positive would affect the involvement of lymph node.