

Kadar VEGF, Interleukin-6, Interleukin-10 dan TNF- α pada Cairan Peritoneum, *Tumor Infiltrating Lymphocyte (TIL)* dan *Lymphovascular Space Invasion (LVSI)* pada Jaringan Tumor Sebagai *Progression-free Survival* Karsinoma Ovarium

ABSTRAK

Latar Belakang: Cairan peritoneum merupakan bahan ideal untuk mengevaluasi tumorigenesis karsinoma ovarium lebih akurat daripada di sirkulasi darah perifer. Sitokin yang disekresi oleh sel-sel imun dan non imun seperti Interleukin-6, interleukin-10, TNF- α , Vascular Endothelial Growth Factor (VEGF) serta *Tumor infiltrating lymphocyte (TIL)* berkorelasi kuat dengan tumorigenesis, perkembangan tumor dan metastasis sehingga mungkin berpengaruh terhadap prognosis dan kekambuhan. *Lymphovascular space invasion (LVSI)* merupakan tahapan penting dalam penyebaran tumor. Prediksi kekambuhan yang pada akhirnya mempengaruhi prognosis dan kesintasan pasien kanker ovarium epithelial sangat mungkin dapat dicapai dengan memantau kadar sitokin dalam asites, persentase TIL dan LVSI jaringan tumor.

Tujuan: Untuk mengetahui hubungan kadar sitokin (IL-6, IL-10, TNF- α dan VEGF) dalam cairan peritoneum, TIL dan LVSI jaringan tumor terhadap *progression-free survival (PFS)* pasien karsinoma ovarium

Metode: Penelitian ini menggunakan desain penelitian kohort prospektif. Subjek penelitian ini adalah pasien yang menderita karsinoma ovarium. Sampel diambil dari cairan asites dan jaringan tumor penderita kanker ovarium tipe epitel yang menjalani operasi primer di RSUP dr Sardjito periode 2018-2021. Luaran PFS dicatat jika muncul progresi atau pada akhir penelitian. Pemeriksaan kadar sitokin dari cairan peritoneum atau asites dilakukan dengan *Human cytokine magnetic 10-plex panel for luminex (commercial kit Invitrogen)* untuk IL-6, IL-10 dan TNF alpha, dan *Human VEGF Quantikine ELISA Kit R&D* untuk VEGF. Pemeriksaan ekspresi TIL dan LVSI jaringan tumor dilakukan dengan pembacaan visual pada preparat patologi anatomi yang dilakukan pengecatan hematoxylin eosin.

Hasil: Terdapat 40 pasien karsinoma ovarium yang menjadi subjek penelitian. Median follow-up adalah 24 bulan dengan follow up terlama 39 bulan. Pada penelitian ini dijumpai 18 (45%) progresi dan 20 (50%) kematian selama follow up. Kadar IL6 cairan peritoneum dan usia yang meningkat berhubungan dengan perburukan PFS baik pada bivariat maupun multivariat dengan masing-masing HR=4,54; 95% CI 1,576-13,059; p=0,005 dan HR=4,72; 95% CI 1,198-18,623; p=0,027. Histopatologi tipe II merupakan prediktor terkuat terhadap perburukan PFS dengan HR=7,27; 95% CI 1,569-33,665; p=0,011. Terdapat hubungan korelasi yang sangat kuat antara IL-6 dan IL-10 (r=0,940). Kadar VEGF, TNF- α cairan peritoneum serta TIL dan LVSI jaringan tumor, stadium, residu tumor, ca 125 preoperasi dan jumlah cairan peritoneum tidak berhubungan dengan PFS (p<0,05)

Kesimpulan: Peningkatan kadar IL-6 cairan peritoneum dan usia serta histopatologi tipe II merupakan prediktor independen perburukan PFS.

Kata kunci: IL-6, IL-10, usia, histopatologi tipe II, karsinoma ovarium, cairan peritoneum, *progression free survival*

Levels of VEGF, Interleukin-6, Interleukin-10, and TNF- α in Peritoneal fluid, Tumor-Infiltrating-Lymphocyte (TIL), and Lymphovascular-Space-Invasion (LVSI) in Tumor Tissue as Predictors of Progression-free survival of Ovarian Carcinoma

ABSTRACT

Backgrounds: Peritoneal fluid is an ideal material for evaluating tumorigenesis of ovarian carcinoma more accurately than in peripheral blood circulation. Cytokines and Tumor-Infiltrating-Lymphocyte (TIL) are strongly correlated with tumorigenesis, tumor development, and metastasis so that they may have an effect on prognosis and recurrence. Lymphovascular space invasion (LVSI) is an important step in tumor dissemination. Prediction of recurrence which ultimately affects the prognosis and survival of patients with epithelial ovarian cancer is very likely to be achieved by monitoring the levels of cytokines in ascites, the percentage of TIL, and LVSI of tumor tissue. This study aims to determine the relationship between levels of cytokines (IL-6, IL-10, TNF- α , VEGF) and PFS.

Methods: This study is a prospective cohort research design. The subjects of this study were patients suffering from ovarian carcinoma. Samples were taken from ascitic fluid and tumor tissue of epithelial-type ovarian cancer patients undergoing primary surgery at Dr. Sardjito General Hospital for the 2018-2021 period. PFS was measured when event happened or in the end of study. Examination of cytokine levels from peritoneal fluid or ascites was performed with the Human cytokine magnetic 10-plex panel for Luminex (commercial kit Invitrogen) for IL-6, IL-10, and TNF- α , and the Human VEGF Quantikine ELISA Kit R&D for VEGF. Examination of TIL and LVSI expression of tumor tissue was carried out by visual reading on anatomical pathology preparations stained with hematoxylin and eosin.

Results: 40 ovarian carcinoma patients were the research subjects. The median follow-up was 24 months with the longest follow-up being 39 months. This study had 18 (45%) progressions and 20 (50%) deaths during follow-up. Increased peritoneal fluid IL6 levels and age are associated with worsening PFS both in bivariate and multivariate with HR=4.54; 95% CI 1.576-13.059; p=0.005 and HR=4.72; 95% CI 1.198-18.623; p=0.027. Type II histopathology is the strongest predictor of worsening PFS with HR=7.27; 95% CI 1.569-33.665; p=0.011. There is a very strong correlation between IL-6 and IL-10 ($r=0.940$). Peritoneal fluid VEGF and TNF- α levels, TIL and LVSI expression of tumor tissue, FIGO stage, residual tumor, pre-operative serum Ca-125 and amount of peritoneal fluid did not associated with progression-free survival (p<0.05)

Conclusion: Increased peritoneal fluid IL-6 levels, age, and type II histopathology are independent predictors of poor PFS.

Keyword: IL-6, IL-10, age, type 2 histopathology, ovarian carcinoma, peritoneal fluid, progression free survival