

## ABSTRACT

### **Background:**

Heparanase activity has important roles in the metastatic of cancer. Single nucleotida polymorphisms (SNPs) in the heparanase (HPSE) gene especially rs4693608 and rs6535455 have been shown to be correlated with various hematological malignancies, gastric cancer and other solid malignancies. Most ovarian tumors were epithelial and clear cell carcinoma was a malignant tumor with the worst prognosis. The present study investigated the characteristics of SNPs rs4693608 and rs6535455 in the HPSE gene among various epithelial ovarian tumor sub-types, and their associations with age, size and location of tumor.

### **Methods:**

DNA was extracted from 65 formaline-fixed paraffin-embedded (FFPE) samples of epithelial ovarian tumor. They consisted of 13 samples for benign group, 16 samples for borderline group and 36 samples for malignant group with various subtypes. The samples were taken from Sardjito Hospital, Yogyakarta, 2014-2016. The SNPs rs4693608 and rs6535455 of HPSE gene were detected using RFLP method. The results were statistically analyzed by Chi-Square and Fisher Exact test.

### **Results:**

This study observed that the rs4693608 wild-type AA-allele had a higher frequency compared to AG and GG-allele in non-malignant and malignant ovarian tumor (72,4% and 74,3%, respectively). The rs6535455 wild-type CC-allele had a higher frequency compared to TC and TT-allele in non-malignant and malignant ovarian tumor (75,91% and 82,1%, respectively). In clear cell carcinoma, there were mutant-type rs4693608 GG alleles in 2 of 35 samples of malignant tumors (5.71%) and mutant-type TT alleles rs6535455 in 1 of 28 samples of malignant tumors (3.57%). In endometrioid carcinoma, there were mutant-type allele TT rs6535455 in 2 of 28 malignant tumor samples (7.14%). In borderline serosum tumors, there were mutant-type allele TT rs6535455 in 1 of 28 of the malignant tumor samples (3.57%). There were no significant difference of SNPs rs4693608 and rs6535455 in HPSE gene between non-malignant and malignant ovarian tumor ( $p=0,866$  and  $p=0,561$ , respectively), and based on age, size and location of the tumor ( $p>0,05$ ) as well.

### **Conclusion:**

The SNPs rs4693608 and rs6535455 in the HPSE gene were no significant difference between non-malignant and malignant ovarian tumor, and between clinicopathological factors. However, this study found mutant-type allele SNP rs4693608 appear only in clear cell carcinoma which is the most malignant variant of epithelial ovarian malignant tumors, while the mutant-type allele SNP rs6535455 was obtained in clear cell carcinoma and endometrioid carcinoma.

### **Keywords:**

Epithelial ovarian tumors; HPSE gene SNPs rs4693608 and rs6535455; Age; Size and location of tumor.

## INTISARI

### Latar belakang :

Heparanase berperan penting pada metastasis kanker. *Single Nucleotide Polymorphism* (SNP) gen heparanase (HPSE) terutama rs4693608 dan rs6535455 terbukti berhubungan dengan berbagai keganasan hematologi, kanker lambung dan keganasan lainnya. Tumor ovarium terbanyak adalah jenis epitelial dan *clear cell carcinoma* merupakan tumor ganas dengan prognosis paling buruk. Penelitian ini meneliti karakteristik SNP rs4693608 dan rs6535455 gen HPSE pada berbagai sub-tipe tumor ovarium epitelial, dan hubungannya dengan usia, ukuran dan lokasi tumor.

### Metode:

Diteliti 65 sampel *formaline-fixed paraffin-embedded* (FFPE) tumor ovarium epitelial, terdiri dari 13 sampel jinak, 16 sampel *borderline* dan 36 sampel ganas dengan berbagai sub-tipe dari RSUP Dr. Sardjito, Yogyakarta, tahun 2014-2016. Sampel diekstraksi DNA dan SNP rs4693608 dan rs6535455 gen HPSE dideteksi menggunakan metode RFLP. Hasil penelitian dianalisis secara statistika dengan uji *Chi-Square* dan *Fisher Exact*.

### Hasil:

Pada penelitian ini didapatkan bahwa frekuensi SNP gen HPSE rs4693608 alel AA *wild-type* lebih tinggi dibandingkan alel AG dan GG baik pada tumor ovarium non-ganas dan ganas (72,4% dan 74,3%). Frekuensi rs6535455 alel CC *wild-type* lebih tinggi dibandingkan dengan alel TC dan TT baik pada tumor ovarium non-ganas dan ganas (75,91% dan 82,1%). Pada *clear cell carcinoma* didapatkan alel GG *mutant-type* rs4693608 sebanyak 2 dari 35 sampel tumor ganas (5,71%) dan alel TT *mutant-type* rs6535455 sebanyak 1 dari 28 sampel tumor ganas (3,57%). Pada karsinoma endometrioid didapatkan alel TT *mutant-type* rs6535455 sebanyak 2 dari 28 sampel tumor ganas (7,14%). Pada tumor serosum *borderline* didapatkan alel TT *mutant-type* rs6535455 sebanyak 1 dari 28 sampel tumor ganas (3,57%). Tidak ada perbedaan yang bermakna SNP rs4693608 dan rs6535455 gen HPSE antara tumor ovarium non-ganas dan ganas ( $p = 0,866$  dan  $p = 0,561$ ), maupun berdasarkan usia, ukuran dan lokasi tumor ( $p > 0,05$ ).

### Kesimpulan:

SNP rs4693608 dan rs6535455 pada gen HPSE tidak berbeda antara tumor ovarium non-ganas dan ganas, maupun antara berbagai faktor klinikopatologi pada tumor ovarium epitelial. Alel *mutant-type* SNP rs4693608 hanya didapatkan pada *clear cell carcinoma* yang merupakan varian paling ganas dari tumor ganas ovarium epitelial, sedangkan alel *mutant-type* SNP rs6535455 didapatkan pada *clear cell carcinoma* dan karsinoma endometrioid.

### Kata kunci:

Tumor ovarium epitelial; SNP gen HPSE rs4693608 dan rs6535455; Usia; Ukuran tumor; Lokasi tumor.