

## ABSTRACT

### **Background:**

Urothelial carcinoma is the most common bladder cancer. Mortality has not decreased with combination cisplatin-based chemotherapy, so alternative therapies are needed. The recently suggested therapy includes immune checkpoint inhibiting agents including anti PD-L1 (Programmed Death Ligand 1). High expression of PD-L1 in bladder cancer was suggested to be associated with HG, disease recurrence, and decreased survival. However, the PD-L1 expression profile among urothelial carcinoma cases in Indonesia and its association with pathological parameters are not widely studied.

### **Objective:**

Determining the expression of PD-L1 in urothelial carcinoma of the bladder at Dr. Sardjito Hospital, Yogyakarta and its association with pathological parameters; grading tumor, proliferation index and tumor-infiltrating lymphocytes (TILs).

### **Methods:**

Seventy formalin-fixed paraffin embedded (FFPE) tissue diagnosed with urothelial bladder carcinoma from Sardjito Hospital in 2015-2019 were consecutively selected as samples and examined PD-L1 expression and Ki-67 with immunohistochemistry. PD-L1 expression was determined by a combined positive score (CPS). PD-L1 antibody was using Clone 22C3. Tumor grade and TILs were observed in HE staining and divided into *low* or *high-grade* based on morphology, TILs is grouped into intense ( $\geq 10\%$ ) and non-intense ( $<10\%$ ). The proliferation index was assessed by counting the number of Ki-67 positive cells per 1,000 tumor cells and presented as a percentage. The results were analysed using the Spearman correlation with the IBM SPSS 25 application.

### **Result:**

PD-L1 was expressed in 8.57% of cases. The number of samples with intense TILs was 46 (65.71%) and 24 (34.28%) non-intense TILs. PD-L1 expression was significantly associated with the proliferation index ( $p = 0.043$ ) and TILs ( $p = 0.032$ ). It was significantly correlated with proliferative index ( $p=0.043$ ) and TILs ( $p=0.032$ ), but not correlated with tumor grade ( $p = 0.236$ ).

### **Conclusion :**

PD-L1 expression in urothelial carcinoma of the bladder was significantly associated with proliferation index and TILs, but not with tumor grade.

**Keywords:** urothelial carcinoma, PD-L1 IHC 22C3, proliferation index, grading tumor, tumor-infiltrating lymphocyte

## INTISARI

### Latar belakang:

Karsinoma urotelial merupakan kanker kandung kemih terbanyak. Mortalitas kanker ini tidak menurun dengan terapi cisplatin berbasis platinum, sehingga diperlukan terapi alternatif. Saat ini dikembangkan terapi berupa agen penghambat *checkpoint* antara lain anti PD-L1 (*Programmed Death Ligan 1*). Profil ekspresi PD-L1 yang tinggi berkaitan dengan *grading* tumor, indeks proliferasi dan *tumor-infiltrating lymphocyte (TILs)* pada karsinoma urotelial kandung kemih di Indonesia belum banyak dikembangkan.

### Objektif:

Mengetahui ekspresi PD-L1 pada karsinoma urotelial kandung kemih dan dengan berbagai parameter patologik, yaitu *grading* tumor, indeks proliferasi dan *TILs*.

### Metode :

Tujuh puluh blok parafin karsinoma urotelial kandung kemih dari RSUP Dr. Sardjito Yogyakarta tahun 2015-2019 dipilih sebagai sampel dan diperiksa ekspresi PD-L1 dan Ki-67 dengan metode imunohistokimia. PD-L1 and Ki-67. Ekspresi PD-L1 ditentukan dengan *combined positive score (CPS)*. Antibodi PD-L1 menggunakan klon 22C3. *Grading* tumor dan *TILs* diamati pada sediaan HE dan dikelompokkan dalam *low* atau *high-grade*, *TILs* dinyatakan dalam intense ( $\geq 10\%$ ) dan non-intense ( $< 10\%$ ). Indeks proliferasi dinilai dengan menghitung jumlah sel yang positif Ki-67 per 1.000 sel dan dinyatakan dalam persentase. Hasil dianalisis menggunakan uji korelasi Spearman dengan perangkat lunak *IBM SPSS 25*.

### Hasil:

PD-L1 terekspresi pada 8,57% kasus. Jumlah *high-grade urothelial carcinoma* lebih banyak (85,71%) dibandingkan dengan *low-grade urothelial carcinoma*. (14,28%). Jumlah sampel dengan *TILs* intense sebanyak 46 (65,71%) dan *TILs* non-intense 24 (34,28%). Ekspresi PD-L1 secara signifikan berhubungan dengan indeks proliferasi ( $p=0.043$ ) dan *TILs* ( $p=0,032$ ). Namun, tidak didapatkan hubungan yang signifikan dengan *grading* tumor ( $p = 0.236$ ).

### Kesimpulan :

Ekspresi PD-L1 pada karsinoma urotelial kandung kemih berhubungan secara signifikan dengan indeks proliferasi dan *TILs*, namun tidak dengan *grading* tumor.

**Kata kunci:** Karsinoma urotelial , PD-L1 IHC 22C3, indeks proliferasi, *tumor grade*, *tumor infiltrating lymphocyte*



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