INTISARI

PERAN PROGNOSTIK *MICROSATELLITE INSTABILITY* (MSI) DAN EKSPRESI *PROGRAMMED DEATH-LIGAND 1* (PD-L1) TERHADAP KESINTASAN HIDUP PASIEN KANKER KOLOREKTAL

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Latar Belakang

Kanker kolorektal (KKR) menempati posisi ketiga sebagai kanker paling sering di dunia dan keempat tersering di Indonesia. Salah satu mekanisme yang memungkinkan KKR untuk terus berproliferasi adalah kemampuannya untuk menghindari pengecekan dari sistem imun. Mekanisme penting penghindaran sistem imun tersebut adalah adanya interaksi antara PD-1 (*programmed death-1*) dan ligannya yaitu PD-L1 (*programmed death ligand-1*). Selain itu ekspresi PD-L1 juga berkaitan dengan *microsatellite instability* (MSI). MSI dan ekspresi PD-L1 diketahui memiliki peran prognostik yang berbeda-beda tergantung stadium dan profil patologi. namun eksplorasi tentang hal ini masih sangat terbatas di Indonesia. Oleh karenanya, penelitian ini bertujuan untuk mengetahui peran prognostik MSI dan PD-L1 terhadap kesintasan hidup pasien KKR.

Metode

Penelitian ini menggunakan desain kohort retrospektif pada pasien KKR yang terdiagnosis antara tahun 2016-2019 di RSUP Dr. Sardjito. Penentuan sampel penelitian menggunakan teknik *purposive sampling* terhadap data dari basis data registri KKR yang sudah ada. Data klinis dan patologis pasien didapatkan dari basis data registri KKR, sedangkan ekspresi PD-L1 dan MSI didapatkan dari pemeriksaan terhadap blok parafin pasien yang tersimpan di laboratorium patologi anatomi. Data kesintasan hidup umum diperoleh dari catatan medik dan komunikasi langsung, dimana masa observasi ditetapkan sampai 31 Agustus 2023. Digunakan metode Kaplan-Meier bersamaan dengan uji log-rank untuk menilai dan membandingkan kesintasan hidup antar kelompok. Regresi c*ox-proportional hazards* digunakan untuk mengidentifikasi faktor-faktor yang mempengaruhi kesintasan hidup dengan $p < 0,05$ dianggap signifikan secara statistik.

Hasil

Penelitian ini melibatkan 72 pasien KKR dimana 26 pasien (36,1%) mengekspresikan PD-L1 positif dan 17 pasien (23,6%) menunjukkan MSI. Median *follow up* adalah 29,5 bulan (0-87 bulan) dengan median kesintasan hidup umum

adalah 14 bulan. Median kesintasan hidup pasien dengan PD-L1 positif adalah 18 bulan dan pasien dengan PD-L1 negatif sebesar 14 bulan (*log rank* p = 0,563). Median kesintasan hidup pasien dengan MSI adalah 15 bulan sedangkan pada *microsatellite stable* (MSS) 14 bulan (*log rank* p = 0,407). Analisis univariat menunjukkan adanya beberapa variabel yang berhubungan dengan kesintasan hidup yaitu indeks massa tubuh (<18,5 kg/$m^{2,}$ p = 0,027, HR = 2,145, IK 95% 1,090-4,221), grading histologi (Grade 3-4, p = 0.002, HR = 3.967, IK 95% = 1,685-9337), CEA (p = 0,029, HR = 2,405, IK 95% = 1,092-5,301), stadium metastasis (p = 0,004, HR = 2,621, IK 95% = 1,372-5,006), terapi sistemik lini pertama (p = 0,047, HR = 1,933, IK 95% = 1,010-3,700) dan terapi sistemik lini kedua (p = 0,046, HR 2,490, IK 95% = 1,017-6,093). Berdasarkan analisis multivariat didapatkan bahwa kesintasan hidup pasien dengan MSI lebih buruk dalam pemodelan bersama histologi grading (p =0,009, HR = 2,817, IK 95% 1,306-6,156)

Kesimpulan

Status MSI berhubungan dengan kesintasan hidup umum yang lebih buruk walaupun bukan faktor prognostik independen. Ekspresi PD-L1 tidak berhubungan dengan kesintasan hidup pasien KKR.

Kata kunci : kanker kolorektal, *microsatellite instability*, *microsatellite stable*, *programmed death ligand-1*

ABSTRACT

THE PROGNOSTIC ROLE OF MICROSATELLITE INSTABILITY (MSI) AND PROGRAMMED DEATH-LIGAND 1 (PD-L1) EXPRESSION IN THE SURVIVAL OF COLORECTAL CANCER PATIENTS

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Background

Colorectal cancer (CRC) ranks as the third most common cancer worldwide and the fourth most frequent in Indonesia. One mechanism that enables CRC to continue proliferating is its ability to evade immune system surveillance. A critical immune evasion mechanism involves the interaction between PD-1 (programmed death-1) and its ligand, PD-L1 (programmed death ligand-1). PD-L1 expression has been observed to associate with microsatellite instability (MSI). The prognostic role of MSI and PD-L1 expression varies depending on stage and pathological profile. Since this topic is very rarely explored in Indonesian cases, we aim to analyse the prognostic role of MSI and PD-L1 in the overall survival of CRC patients.

Methods

This study employed a retrospective cohort design involving CRC patients diagnosed between 2016 and 2019 at Dr. Sardjito General Hospital. Sample selection was conducted using purposive sampling on data retrieved from the existing CRC registry. Clinical and pathological data were obtained from the registry database, while PD-L1 expression and MSI status were examined on paraffin blocks stored in the pathology laboratory. The patient survival were obtained from medical record and by phone communication. Observation period for overall survival was set until August 31, 2023. The Kaplan-Meier method was used along with the log-rank test to assess survival and to compare different groups. Cox proportional hazards regression was applied to identify factors affecting survival, with $p < 0.05$ considered as statistically significance.

Results

The study included 72 CRC patients, with 26 (36.1%) expressing positive PD-L1 and 17 (23.6%) MSI. The median follow-up duration was 29.5 months (0-87 months), with a median survival of 14 months. The median survival for patients with positive PD-L1 was 18 months, and for those with negative PD-L1 was 14 months (log-rank $p = 0.563$). The median survival for patients with MSI was 15 months, compared to 14 months for microsatellite stable (MSS) (log-rank p =

0.407). Univariate analysis indicated several variables that associated with survival, including body mass indeks (<18.5 kg/m^2, p = 0.027, HR = 2.145,95% CI = 1,090-4,221), histological grading (Grade 3-4, p = 0.002, HR = 3.967, 95% CI = 1.685-9.337), CEA (p = 0.029, HR = 2.405,95% CI = 1.092-5.301), metastastic stage (p = 0.004, HR = 2.621, 95% CI = 1.372-5.006), first line systemic therapy (p = 0.047, HR = 1.933, 95% CI = 1.010-3.700) and second line systemic therapy (p = 0,046, HR 2,490, IK 95% = 1,017-6,093). Multivariate analysis of PD-L1 expression, microsatellite status, and significant variables from univariate analysis was performed. Based on multivariable analysis, the survival of patients with MSI was unfavorable in the model incorporating histological grading (p = 0.009, HR = 2.817, 95% CI 1.306–6.156).

Conclusion
MSI status is associated with an unfavorable survival although it is not an independent prognostic factor. PD-L1 expression is not associated with CRC patient survival.

Keywords: colorectal cancer, microsatellite instability, microsatellite stable, programmed death ligand-1