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Profile of Programmed Death Ligand-1 (PD-L1) Expression and PD-L1 Gene Amplification in Indonesian Colorectal Cancer Patients

Authors : Akterono Budiyati, Gita Kusumo, Teguh Putra, Fritzie Rexana, Antonius Kurniawan, Aru Sudoyo, Ahmad Utomo, Andi Utama

Abstract : The presence of the programmed death ligand-1 (PD-L1) has been used in multiple clinical trials and approved as biomarker for selecting patients more likely to respond to immune checkpoint inhibitors. However, the expression of PD-L1 is regulated in different ways, which leads to a different significance of its presence. Positive PD-L1 within tumors may result from two mechanisms, induced PD-L1 expression by T-cell presence or genetic mechanism that lead to constitutive PD-L1 expression. Amplification of PD-L1 genes was found as one of genetic mechanism which causes an increase in PD-L1 expression. In case of colorectal cancer (CRC), targeting immune checkpoint inhibitor has been recommended for patients with microsatellite instable (MSI). Although the correlation between PD-L1 expression and MSI status has been widely studied, so far the precise mechanism of PD-L1 gene activation in CRC patients, particularly in MSI population have yet to be clarified. In this present study we have profiled 61 archived formalin fixed paraffin embedded CRC specimens of patients from Medistra Hospital, Jakarta admitted in 2010 - 2016. Immunohistochemistry was performed to measure expression of PD-L1 in tumor cells as well as MSI status using antibodies against PD-L1 and MMR (MLH1, MSH2, PMS2 and MSH6), respectively. PD-L1 expression was measured on tumor cells with cut off of 1% whereas loss of nuclear MMR protein expressions in tumor cells but not in normal or stromal cells indicated presence of MSI. Subset of PD-L1 positive patients was then assessed for copy number variations (CNVs) using single Tube TaqMan Copy Number Assays Gene CD247PD-L1. We also observed KRAS mutation to profile possible genetic mechanism leading to the presence or absence of PD-L1 expression. Analysis of 61 CRC patients revealed 15 patients (24%) expressed PD-L1 on their tumor cell membranes. The prevalence of surface membrane PD-L1 was significantly higher in patients with MSI (87%; 7/8) compared to patients with microsatellite stable (MSS) (15%; 8/53) (P=0.001). Although amplification of PD-L1 gene was not found among PD-L1 positive patients, low-level amplification of PD-L1 gene was commonly observed in MSS patients (75%; 6/8) than in MSI patients (43%; 3/7). Additionally, we found 26% of CRC patients harbored KRAS mutations (16/61), so far the distribution of KRAS status did not correlate with PD-L1 expression. Our data suggest genetic mechanism through amplification of PD-L1 seems not to be the mechanism underlying upregulation of PD-L1 expression in CRC patients. However, further studies are warranted to confirm the results.

Keywords : colorectal cancer, gene amplification, microsatellite instable, programmed death ligand-1
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