ABSTRACT

Background: Melanoma is a rare skin malignancy that has a high risk of metastasis. Limited treatment options and resistance of existing treatments lead to a high mortality rate. Although KRAS mutations are rarely reported in melanoma, their presence might cause a resistance to BRAF inhibitor. Synergistic inhibition of both KRAS and BRAF may overcome the resistance to BRAF inhibitor, as reported in a recent study. However, there was no valid data regarding the frequency of KRAS mutation and its clinicopathological characteristics of primary cutaneous melanoma in Indonesia.

Objective: This study aims to identify KRAS mutations status of local primary skin melanoma cases and its association with tumor depth, ulceration, mitotic index, necrosis, lymphovascular invasion and tumor infiltrating lymphocytes (TILs).

Method: Sixty three (63) melanoma samples in formalin-fixed paraffin-embedded (FFPE) were retrospectively taken from the Department of Anatomical Pathology, Dr. Sardjito Hospital, Sleman, Yogyakarta, and dr. Soeradji Tirtonegoro Hospital, Klaten, Central Java from 2011-2020. DNA samples were extracted and KRAS mutations were detected using qualitative real time PCR. The association of KRAS mutation with tumor depth, ulceration, mitotic index, necrosis, lymphovascular invasion and TILs were statitical analyzed by Fisher's exact test (IBMM SPSS software, 23th version).

Result: KRAS mutations were detected in 19.0% (12/63) samples, which comprise of 91.7% (11/12) in exon 2, 4 in codon G12 (33.3%), 2 in codon G13 (16.6%) and 5 in codon G12/13 (41.6%), while 8.3% (1/12) in exon 3 (Q61). These mutations were no significant associated with tumor thickness ($p = 0.33$), ulceration ($p = 0.31$), mitotic index ($p = 1.00$), necrosis ($p = 0.73$), lymphovascular invasion ($p = 0.33$) and TILs ($p = 0.45$).

Conclusion: The higher prevalence of KRAS mutations in our local population compared to other countries needs a special attention, especially mutations at codon 12 are more aggressive. In this sudy, KRAS mutations were not associated with tumor depth, ulceration, mitotic index, necrosis, lymphovascular invasion, and TILs in primary skin melanoma.

Keywords: Melanoma, KRAS mutations, tumor depth, ulceration, mitotic index, necrosis, lymphovascular invasion and TILs.

ABSTRAK

Latar belakang: Melanoma adalah keganasan kulit langka yang memiliki risiko tinggi untuk bermetastasis. Pilihan pengobatan yang terbatas dan resistensi terhadap pengobatan yang ada menyebabkan tingginya tingkat kematian. Meskipun mutasi KRAS jarang dilaporkan pada melanoma, kehadirannya dapat menyebabkan resistensi terhadap BRAF *inhibitor*. Penghambatan sinergis dari KRAS dan BRAF dapat mengatasi resistensi terhadap BRAF *inhibitor*, seperti yang dilaporkan dalam penelitian terbaru. Namun, belum ada data yang valid mengenai frekuensi mutasi KRAS dan karakteristik klinikopatologinya pada melanoma kulit primer di Indonesia.

Objektif: Penelitian ini bertujuan untuk mengidentifikasi status mutasi KRAS pada kasus melanoma kulit primer di Indonesia dan hubungannya dengan kedalaman tumor, ulserasi, indeks mitosis, nekrosis, invasi limfovaskular dan *tumor infiltrating lymphocytes (TILs)*.

Metode: Enam puluh tiga (63) sampel melanoma dalam bentuk *formalin-fixed paraffin-embedded* (FFPE) dikumpulkan secara retrospektif dari Instalasi Patologi Anatomi Rumah Sakit Umum Pusat (RSUP) Dr. Sardjito, Sleman, Yogyakarta dan dr. Soeradji Tirtonegoro, Klaten, Jawa Tengah pada periode tahun 2011 – 2020. DNA sampel diekstraksi dan mutasi KRAS dideteksi dengan *qualitative real time*-PCR (qRT-PCR). Hubungan mutasi KRAS dengan kedalaman tumor, ulserasi, indeks mitosis, nekrosis, invasi limfovaskular dan *TILs* dianalisis dengan uji statistik *uji Fisher's exact* (IBMM SPSS *software*, *23th version*).

Hasil: Mutasi KRAS terdeteksi pada 19,0% (12/63) sampel, 91,7% (11/12) pada ekson 2, di antaranya 4 pada kodon G12 (33,3%), 2 pada kodon G13 (16,6%) dan 5 pada kodon G12/13 (41,6%). Mutasi ini tidak berhubungan secara signifikan dengan kedalaman tumor (p = 0,33), ulserasi (p = 0,31), indeks mitosis (p = 1,00), nekrosis (p = 0,73), invasi limfovaskular (p = 0,33), dan *TILs* (p = 0,45).

Kesimpulan: Tingginya prevalensi mutasi KRAS pada populasi lokal dibandingkan dengan negara lain patut mendapat perhatian, terlebih mutasi pada kodon 12 yang bersifat lebih agresif. Pada penelitian ini mutasi KRAS tidak berhubungan dengan kedalaman tumor, ulserasi, indeks mitosis, nekrosis, invasi limfovaskular, dan *TILs* pada melanoma kulit primer.

Kata kunci: Melanoma kulit, mutasi KRAS, kedalaman tumor, ulserasi, indeks mitosis, nekrosis, invasi limfovaskuler dan *TILs*.