

# Pengaruh Melatonin terhadap Respons Klinis Karsinoma Sel Skuamosa Rongga Mulut Stadium Lanjut Lokal yang Diberi Kemoterapi Neoadjuvan: Kajian terhadap Ekspresi HIF-1 $\alpha$ , CD44, CD133, dan miR-210 = The Effect of Melatonin in Combination with Neoadjuvant Chemotherapy to the Clinical Response of Squamous Cell Carcinoma of Locally Advanced Oral Cancer: a study on HIF-1 $\alpha$ , CD44, CD133, and miR-210

Diani Kartini, author

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## Abstrak

Karsinoma sel skuamosa rongga mulut (KSS-RM) merupakan keganasan yang menempati urutan ke-6 dari seluruh kasus kanker di dunia. Pembedahan merupakan terapi utama KSS-RM namun pada KSS-RM lanjut lokal, pembedahan merupakan tantangan bagi dokter bedah karena struktur anatomi yang rumit dan dampaknya terhadap kualitas hidup penderita. Oleh karena itu dipikirkan pemberian kemoterapi neoadjuvan (KN) pada KSS-RM stadium lanjut lokal untuk mengecilkan tumor. Kemoresistensi merupakan masalah pemberian KN pada KSS-RM stadium lanjut lokal akibat microenvironment yang hipoksik ditandai dengan peningkatan ekspresi HIF-1 $\alpha$ . Kemoresistensi juga diregulasi oleh miR-210 serta peningkatan ekspresi penanda sel punca CD44 dan CD133. Melatonin memiliki efek antioksidan kuat dan efek onkostatik sehingga diharapkan dapat memperbaiki kondisi hipoksia tumor. Penelitian ini merupakan uji klinis dengan desain paralel acak tersamar pembanding plasebo, yang dilaksanakan pada bulan Juni 2017 hingga Juli 2018, bertujuan untuk mengetahui efektivitas melatonin dalam meningkatkan respons klinis penderita KSS-RM stadium lanjut lokal yang diberikan kemoterapi neoadjuvan dan apakah melatonin dapat memperbaiki hipoksia yang ditandai dengan penurunan ekspresi HIF-1 $\alpha$ , miR-210, CD44, dan CD133. Sebanyak 50 pasien KSS-RM stadium lanjut lokal dari RSCM dan RSKD dirandomisasi. Sebanyak 25 pasien mendapat kombinasi melatonin dan KN (taksan, sisplatin, dan 5-fluorourasil) dan 25 pasien lainnya mendapat KN saja. Sebanyak 25 pasien yang menyelesaikan protokol penelitian (13 pasien kelompok melatonin dan 12 pasien kelompok plasebo). Perubahan ekspresi HIF-1 $\alpha$ , miR-210, CD44, dan CD133 yang diukur dari jaringan biopsi sebelum terapi dan jaringan biopsi/eksisi luas pasca terapi, menggunakan metode qRT-PCR absolute quantification. Selain itu untuk menilai respons klinis digunakan RECIST 1.1 sebelum dan sesudah KN. Melatonin 20 mg perhari menurunkan ekspresi HIF-1 $\alpha$  ( $p = 0,301$ ), miR-210 ( $p = 0,767$ ), dan CD44 ( $p = 0,103$ ) namun tidak bermakna jika dibandingkan plasebo. Ekspresi CD133 meningkat pada kedua kelompok melatonin dan plasebo ( $p = 0,301$ ) walaupun tidak bermakna. Melatonin 20 mg perhari selama 1 minggu sebelum KN pertama dimulai sampai KN selesai tidak memberikan perbedaan respons positif yang bermakna pada dua kelompok. Penurunan konsentrasi HIF-1 $\alpha$  dan CD133 tidak diikuti penurunan persentase sisa tumor. Pada kelompok melatonin, ekspresi CD44 dan miR-210 menurun diikuti penurunan persentase sisa tumor yang tidak bermakna dibandingkan plasebo. Pada kelompok yang mendapat melatonin, persentase sisa tumor 21,35% lebih rendah dibandingkan kelompok plasebo meskipun tidak berbeda bermakna ( $p = 0,531$ ).

Squamous cell carcinoma of the oral cancer

(OSCC) is the sixth most common malignancy of all malignant tumors. Surgery is the mainstay of treatment for oral cavity cancers. Surgery in locally advanced OSCC presents many challenges primarily because the head and neck region have many critical structures that can be damaged by tumor or treatment. Damage to these structures can result in significant structural, cosmetic and functional deficits that negatively impact quality of life. Therefore, it is thought that neoadjuvant chemotherapy (KN) in local advanced stage OSCC is to shrink the tumor. The chemoresistance is a problem of KN administration in locally advanced OSCC due to a hypoxic microenvironment characterized by increased expression of HIF-1 $\alpha$ . The chemoresistance is also regulated by miR-210 as well as increased expression of CD44 and CD133 stem cell markers. Melatonin has powerful antioxidant effects and oncostatic effects that are expected to improve tumor hypoxia. This study is a double-blind, randomized clinical trial, which was carried out in June 2017 to July 2018 to determine the effectiveness of melatonin in improving the clinical response of locally advanced OSCC patients given neoadjuvant chemotherapy and whether melatonin can improve hypoxia marked by decreased expression of HIF-1 $\alpha$ , miR-210, CD44, and CD133. Only 25 patients had completed the study protocol, 13 in melatonin group and 12 in placebo group. The difference in HIF-1 $\alpha$ , miR-210, CD44, and CD133 expression were measured as a  $\Delta$  concentration using absolute quantification qRT-PCR. The concentration of the biomolecular markers within the tumor tissue taken from the first biopsy (pretreatment) were determined using qRT-PCR then subtracted from the concentration of biomarkers taken from the second biopsy. The clinical response was assessed using RECIST 1.1. The administration of melatonin 20 mg/day decreased the expression of HIF-1 $\alpha$  ( $p = 0,301$ ), miR-210 ( $p = 0,767$ ), and CD44 ( $p = 0,103$ ) but not statistically significant. CD133 expression increased in both group melatonin and placebo ( $p = 0,301$ ). Melatonin 20 mg per day for 1 week before NC was started until NC was completed did not give a significant difference in positive responses in the two groups. The decrease concentrations of HIF-1 and CD133 were not followed by a decrease in the percentage of remaining tumors. The melatonin group showed a decrement in CD44 and miR-210 followed by a decrement in the percentage of remaining tumors that were not significant compared to placebo. In this study, melatonin did not increase the clinical response although there is 21.35% decrement in tumor mass in melatonin group compare ( $p = 0,531$ ).