Pengaruh Melatonin terhadap Respons Klinis Karsinoma Sel Skuamosa Rongga Mulut Stadium Lanjut Lokal yang Diberi Kemoterapi Neoadjuvan: Kajian terhadap Ekspresi HIF-1?, 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- 1Î±, CD44, CD133, and miR-210

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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-1Î±. 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-1Î±, 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-1Î±, 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-1Î± (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-
1a 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). <hr /> 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 chemoresistancy is a
problem of KN administration in locally advanced OSCC due to a hypoxic
microenvironment characterized by increased expression of HIF-1Î±. The
chemoresistancy 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-1Î±, 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-1Î±, 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-1Î±
(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).</p>