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Pengaruh Pola Radiasi yang Mengikuti Sirkadian terhadap Respons Radioterapi Kanker Serviks Uteri: Melatonin dan Fase Siklus Sel sebagai Marka Biologi dan Radiosensitivitas = Influence of Radiation Patterns Following Circadian Rhythm upon Response of Radiotherapy of Uterine Cervix Cancer: Melatonin and Cycle Cell Phase as Biological Marker and Radiosensitivity

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Abstrak

Respons radiasi kanker serviks diduga dapat ditingkatkan dengan pemilihan waktu radiasi tetap yang berpola sirkadian karena dianggap sesuai dengan fase radiosensitif G₂-M sel kanker. Daur sirkadian dan melatonin dianggap berperan dalam radiosensitivitas. Dihipotesiskan respons radiasi pagi hari maupun efek samping radiasi pagi hari akan lebih baik dibanding sore hari. Penelitian ini merupakan uji klinis dengan perolehan subjek secara berurutan. Alokasi pilihan waktu radiasi pada pagi (06.00–08.00) dan sore (16.00–18.00) hari dengan randomisasi blok tiap enam subjek terpisah antara stadium II dan III. Data diperoleh menggunakan metode open label. Pengukuran data klinis seperti ukuran tumor, respons klinis, dan efek samping dilakukan oleh dua dokter independen yang terlatih. Dilakukan pengukuran kadar melatonin dan fase G₂-M siklus sel di institusi resmi. Respons baik dan buruk ditetapkan berdasarkan kriteria WHO sedangkan efek samping ada atau tidak, ditetapkan berdasarkan kiriteria RTOG. Penyinaran di waktu pagi menunjukkan respons klinis lebih baik dibandingkan sore (p 0,025; 95% IK:1,27–33,08; adj OR: 6,48) untuk respons pascaradiasi maupun 2–4 minggu pascaradiasi (p 0,048; 95% IK 1,02–47,81; adj OR 6,98). Kadar Hb awal dan ukuran klinis tumor berpengaruh secara bermakna terhadap respons baik pascaradiasi maupun respons baik 2–4 minggu pascaradiasi. Dalam hal efek samping, pilihan waktu radiasi tidak menunjukkan hasil yang bermakna, namun kadar melatonin praradiasi berpengaruh, khususnya efek samping kulit (p 0,006; 95% IK 1,66–18,99; adj OR 5,62). Variabel yang bermakna memengaruhi efek samping terapi pada gastrointestinal adalah overall treatment time (p 0,031; 95% IK 1,19–39,93; adj OR 6,89), sedangkan untuk genitourinaria adalah PA diferensiasi (p 0,015; 95% IK 1,51–46,37; adj OR 8,36), penurunan berat badan (p 0,025; 95% IK 1,22–18,30; adj OR 4,72), dan nyeri sebelum radiasi (p 0,017; 95% IK 1,31–15,32; adj OR 4,47). Simpulan: Respons radiasi kanker serviks uteri yang diradiasi pagi hari lebih baik daripada yang diradiasi sore hari, namun efek samping radiasi pagi hari tidak berbeda bermakna dibandingkan sore hari. Belum dapat dipastikan pengaruh besarnya proporsi fase G₂-M terhadap respons klinis radiasi. Ada kecenderungan pengaruh kadar melatonin pagi hari terhadap respons klinis radiasi dan terbukti kadar melatonin berpengaruh pada efek samping kulit. Kata kunci: kanker serviks, melatonin, radiosensitivitas, siklus sel, sirkadian <hr /> The radiation response of cervical cancer can be enhanced by the choice of a fixed radiation time of circadian pattern because it is considered to be in accordance with the radiosensitive phase of G₂-M cancer cells. Circadian cycles and melatonin are thought to play a role in radiosensitivity. It is hypothesized that the response and side effects of morning radiation will be better than the afternoon. This study was an RCT (randomized clinical trials) with consecutive sampling.

Treatment allocation for radiation time in the morning (06.00–08.00) and afternoon (16.00–18.00) were determined by block randomization for every six subjects based on the stage (II and III). The data was obtained with an open label method. Measurement of clinical data such as tumor size, clinical response, and side effects were carried out by two-trained independent physicians. Measurement of melatonin levels and G₂-M phases of cell cycle were carried out in official institution. Good and poor responses were set based on WHO criteria while the side effects were determined based on the RTOG criteria. Morning radiation showed a better post-radiation and 2–4 weeks post-radiation clinical response compared with afternoon (p 0.025; 95% CI:1.27–33.08; adj OR: 6.48 and p 0.048; 95%CI 1.02–47.81; adj OR 6.98, respectively). The initial Hb level and clinical size of the tumor had a significant effect on good response both post-radiation and 2-4 weeks post-radiation. In regards to the side effects, radiation time did not show significant results in causing side effects, but pre-radiation melatonin level did on skin (p 0.006; 95%CI 1.66–18.99; adj OR 5.62). The significant variable in influencing gastrointestinal side effects was overall treatment time (p 0.031; 95%CI 1.19–3.93; adj OR 6.89), whereas for genitourinaria were differentiation of histopathology (p 0.015; 95%CI 1.51–46.37; adj OR 8.36), weight loss (p 0.025; 95%CI 1.22–18.30; adj OR 4.72), and presence of pain pre-radiation (p 0.017; 95%CI 1.31–15.32; adj OR 4.47). Conclusion: The radiation response of irradiated uterine cervical cancer is better in the morning than the afternoon. Nevertheless, the side effects of morning radiation do not differ significantly compared to the afternoon. The influence of the G₂-M phase proportion on the clinical response to radiation cannot be ascertained. The level of melatonin in the morning might affect the radiation response and affect the side effects on skin. Keywords: cell cycle, cervical cancer, circadian, melatonin, radiosensitivity.