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Letter to the editors/Reply

Marker rhythms for chronotherapy of cancer

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The article by Bjarnason et al., "Phase I study of 5-fluorouracil (5-FU) and leucovorin (LV) by a 14-day circadian infusion in metastatic adenocarcinoma patients," addresses biological rhythm-dependent differences in drug toxicity.

The purpose of this and other such studies is to determine the optimal circadian patterning of cancer pharmacotherapy. Ideally, sensitive markers of the patient's endogenous circadian time structure, such as the peak time of the cortisol, melatonin, or body-temperature 24-h rhythms, are sought for referencing the administration of circadian rhythm-adapted cancer chronotherapy. However, this is not easily accomplished in clinical settings at present. Thus, surrogate indices of the circadian time structure must be employed.

The staging of the majority of human circadian rhythms is set or reset daily by the activity-in-light/sleep-in-darkness 24-h routine [2, 4]. In the paper by Bjarnason et al., the Materials and methods section states that "patients on a normal activity/sleep routine were entered on study." Undoubtedly, the rationale for including this information on the patient's sleep/activity routine was to provide a temporal reference system for contrasting the relative tolerance of the two circadian-patterned 5-FU/LV pharmacotherapies. The authors found the 24-h sinusoidal shaped continuous-infusion pattern that peaked between 9 and 10 p.m., a clock time that seemingly approximated bedtime, to be less toxic than the one that peaked between 3 and 4 a.m., a clock time that roughly approximated midsleep. In terms of biological time, the tolerance to 5-FU/LV was best when the circadian infusion pattern reached its peak around bedtime as opposed to midsleep.

The authors give the impression that 5-FU/LV toxicity is related *solely* to clock hour rather than circadian-rhythm determinants. This is not the case. The clocking of 5-FU/LV with reference to external time is unacceptable. It is likely to result in the misapplication of circadian cancer chronotherapies, particularly in patients who adhere to sleep-wake routines that differ appreciably from that of the sample studied. Clock time is not indicative of biological time!

Our patient studies utilizing actigraphy [1], a wristwatch-sized device that assesses activity level on a minute-to-minute basis, reveal that some cancer patients retire to bed quite early, 8:30–9:30 p.m., and awake early, 4:30–5:30 a.m., whereas others exhibit a more typical sleep-activity routine. Thus, one cannot optimally apply circadian chronotherapy to cancer patients without individualizing it to each patient's unique time structure as gauged by one's sleep-activity and/or marker (e.g., melatonin, cortisol, or temperature) rhythms. This point is central to the successful implementation of cancer chronotherapies for the control of drug toxicity and enhancement of dose intensity. The implementation of chronotherapeutic strategies to control adverse and/or optimize desired effects is not unique to oncology practice. Several are commonly utilized in the clinic at present, for example, evening theophylline dosing for nocturnal asthma, evening H_2-receptor antagonist medication for peptic ulcer disease, morning corticosteroid tablet treatment for inflammatory conditions, and circadian-rhythm-adapted tocolytic infusion therapy for preterm labor, to mention but a few [3].

References

1. Brown AC, Smolensky MH (1990) Actigraphy: a means of assessing circadian patterns in human activity. Chronobiol Int 7: 125
2. Halberg F, Simpson H (1967) Circadian acrophases of human 17-hydroxycorticosteroid excretion referred to midsleep rather than to midnight. Hum Biol 39: 405
3. Lemmer B (ed) (1989) Chronopharmacology. Cellular and biochemical interactions. Marcel Dekker, New York
4. Wever R, Polasek J, Wildgruber C (1983) Bright light affects human circadian rhythms. Pflugers Arch 396: 85

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