Reply to letter by M. Smolensky and L. T. Campos

Georg A. Bjarnason

Division of Medical Oncology and Clinical Pharmacology, Toronto-Bayview Regional Cancer Center and Sunnybrook Health Science Center, University of Toronto, Toronto, Ontario, Canada

Received/Accepted: 18 February 1994

To the editor: I appreciate the opportunity to respond to Drs. Smolensky and Campos' comments on my paper [1]. They make a very valid point about the importance of marker rhythms in determining the biological time for patients receiving time-modified therapy and the importance of sleep onset as a surrogate marker. We have indeed discussed the importance of this issue in some recent reviews on cancer chronotherapy [9, 10]. Since time-modified therapy remains unfamiliar to most oncologists, the argument for emphasizing the importance of biological time versus clock time in each chronotherapy publication may be valid at the present time.

Most clinical studies of chronochemotherapy have entered patients reporting a "normal" activity/sleep routine without monitoring specific marker rhythms. This may understandably entail a ± 2 h difference in sleep onset. Using this imperfect surrogate measure of biological time and delivering the chemotherapy according to a specified clock time, impressive results have been documented with regard to both time-dependent toxicity and attainable dose intensity [9]. Continuous monitoring of activity via actigraphy provides another indirect measure of biological time [3]. Clinical data are not available, however, to suggest a direct relationship between activity rhythms and rhythms in toxicity and activity for cancer drugs. The use of sleep onset alone as a surrogate marker in cancer patients may be misleading and incomplete. Several other factors, including pharmacogenetics, gender, age, race, tumor burden, performance status, and indeed other cancer drugs and steroids, may affect the internal biological rhythms that impact on the pharmacokinetics and pharmacodynamics of cancer drugs [13]. Hrushesky et al. [11] have studied marker rhythms in cancer patients with small and large tumor burdens. Oral temperature, heart rate, and blood pressure were found to be poor reference rhythms. The cortisol rhythm was affected by both tumor burden and performance status. Urinary volume and sodium excretion rhythms were affected by tumor burden. The rhythm characteristic of urinary potassium excretion was the most stable reference rhythm in this patient population.

The circadian activity of dihydropyrimidine dehydrogenase (DPD), the main 5-fluorouracil (5-FU) catabolic enzyme, might serve as a 5-FU-specific marker rhythm [7]. An inverse relationship between DPD activity in peripheral blood mononuclear cells and plasma 5-FU concentration has been demonstrated in patients receiving a protracted continuous infusion of 5-FU [7]. The importance of DPD activity in determining toxicity from fluoropyrimidines is suggested by the extreme toxicity seen in DPD-deficient patients [8]. This observation emphasizes that pharmacogenetic differences may far outweigh the importance of treatment timing with regard to toxicity. Unfortunately, the use of DPD activity to determine treatment time would be very costly and not transferable to the general oncology community. More recently it has become clear in experimental studies that the menstrual cycle stage of 5-FU therapy may impact on both marrow toxicity [16] and subsequent fertility [17], emphasizing the importance of gender variability.

As we discussed in our paper, that only two treatment times were tested is also of concern. Even though the times chosen were based on some experimental and clinical data, our assumption based on those data could lead to far larger errors with regard to determining a "best time" for 5-FU therapy than does the 2- to 3-h interindividual variation in sleep onset. A six-arm prospective study comparing toxicity and therapeutic acticity at six different treatment times is the only trial design that may answer chronotherapy questions adequately for any drug in any disease process [10]. Ideally this should be combined with the monitoring of both disease- and drug-specific marker rhythms.

Rather than attempting to tailor time-modified therapy to each individual's internal biology, one might attempt to synchronize a patient's biological time to a common clock hour. Several studies have shown that bright light pulses delivered over three or more successive cycles can phase-shift the human circadian timing system [4, 5, 12]. Clinical trials conducted in patients with circadian-related sleep disorders [14], seasonal mood disorders [2], and Alzheimer's disease [15] and in shift workers [6] have documented that phase-shifting can be achieved and used with clinical benefit in these disorders. Convenient light sources are now commercially available that can deliver timed doses of high-intensity light to patients. Light therapy might synchronize and stabilize the circadian time structure of patients receiving time-modified therapy and increase the potential benefits of this scheduling method even more. This has not been attempted in clinical trials of cancer chronotherapy to date.

We have alot to learn with regard to circadian delivery of chemotherapy. Hopefully our small contribution to this field will get other investigators interested in further refining and evaluating this scheduling method.

References

1. Bjarnason GA, Kerr I, Doyle N, Macdonald M, Sone M (1993) Phase I study of 5-fluorouracil and leucovorin by a 14 day cir-

cadian infusion in patients with metastatic adenocarcinoma. Cancer Chemother Pharmacol 33: 221
2. Blehar MC, Lewy AJ (1990) Seasonal mood disorders; consensus and controversy. Psychopharmacol Bull 26: 465
3. Brown AC, Smolensky MH, D'Alonzo GE, Redman DP (1990) Actigraphy: a means of assessing circadian patterns in human activity. Chronobiol Int 7: 125
4. Czeisler CA, Allan JS, Strogatz SH, Ronda JM, Sanchez R, Rios CD, Freitag WO, Richardson GS, Kronauer RE (1986) Bright light resets the human circadian pacemaker independent of the timing of sleep-wake cycle. Science 233: 667
5. Czeisler CA, Kronauer RE, Allan JS, Duffy JF, Jewett ME, Brown EN, Ronda JM (1989) Bright light induction of strong (type 0) resetting of the human circadian pacemaker. Science 244: 1328
6. Czeisler CA, Johnson MP, Duffy JF, Brown EN, Ronda JM, Kronauer RE (1990) Exposure to bright light and darkness to treat physiologic maladaption to night work. N Engl J Med 322: 1253
7. Harris BE, Song R, Soong SJ, Diasio RB (1990) Relationship between dihydropyrimidine dehydrogenase activity and plasma 5-fluorouracil levels with evidence for circadian variation of enzyme activity and plasma drug levels in cancer patients receiving 5-fluorouracil by protracted continuous infusion. Cancer Res 50: 197
8. Harris BE, Carpenter JT, Diasio RB (1991) Severe 5-fluorouracil toxicity secondary to dihydropyrimidine dehydrogenase deficiency. A potentially more common pharmacogenetic syndrome. Cancer 68: 499
9. Hrushesky WJM, Bjarnason GA (1993) The application of circadian chronobiology to cancer chemotherapy. In: DeVita VT, Hellman S, Rosenberg SA (eds) Cancer principles and practice of oncology. J. B. Lippincott, Philadelphia, p 2666
10. Hrushesky WJM, Bjarnason GA (1993) Circadian cancer therapy. J Clin Oncol 11: 1403
11. Hrushesky WJM, Haus E, Lakatua DJ, Halberg F, Langevin T, Kennedy BJ (1985) Marker rhythms for cancer chrono-chemotherapy. In: Haus E, Kabat HF (eds) Chronobiology 1982–1983. Krager, New York, p 493
12. Minors DS, Waterhause JM, Wirz-Justice A (1991) A human phase-response curve to light. Neurosci Lett 133: 36
13. Reinberg AE, Ashkenazi IE (1993) Interindividual differences in chronopharmacologic effects of drugs: a background for individualization of chronotherapy. Chronobiol Int 10: 449
14. Rosenthal NE, Joseph-Vanderpool JR, Levendosky AA, Johnston SH, Allen R, Kelly KA, Souetre E, Schultz PM, Starz KE (1990) Phase-shifting effects of bright morning light as treatment for delayed sleep phase syndrome. Sleep 13: 354
15. Satlin A, Volicer L, Ross V, Herz L, Campbell S (1992) Bright light treatment of behavioral and sleep disturbances in patients with Alzheimer's disease. Am J Psychiatry 149: 1028
16. Vyzula R, Hrushesky WJM, Wood PA, Abruzzese M, Borhan-Manesh S, Penna S de la, Samuel S (1993) Fertility cycle timing of 5-FU determines the severity of its hematological toxicity (abstract VII-7). Proceedings, International Society for Chronobiology, Conference-XXI, Quebec City, July 11–15
17. Whitaker J, Vyzula R, Clooney M, Abruzzese M, Sánchez S, Wood P, Hrushesky WJM (1992) Fertility cycle phase of cytotoxic therapy affects subsequent fertility (abstract A139). Proceedings, 3rd meeting of the Society for Research on Biological Rhythms, Amelia Island Plantation, May 6–10