OncoExpert (2015), Vol. 1, Issue 1 ***Review Article***

OncoExpert
INTERNATIONAL JOURNAL OF INTEGRATED ONCOLOGY

Received on 1 December, 2014; received in revised form, 9 December, 2014; accepted, 24 December, 2014

CANCER CHRONOTHERAPY: THE RIGHT TIME TO HIT!

Ashok Kumar Chauhan[1], Yashpal Verma[2], Ramesh Sabharwal[3]

[1] Senior Professor, Department of Radiotherapy, PGIMS, Rohtak (India)

[2] Medical Officer, Department of Radiotherapy, PGIMS, Rohtak (India)

[3] Medical Officer, General Hospital, Kurukshetra, (India)

Keywords:
Chronomodulation, Chronotherapy, Cancer, Chronobiology, Circadian Rhythm.

Corresponding author:

Dr Yashpal Verma,
Medical Officer,
Department of Radiotherapy,
Post graduate institute of medical sciences,
Rohtak (INDIA).

Email Id: yashpverma@gmail.com

Abstract: Chronomodulated therapy or chronotherapy has gained popularity, beyond a fancy term, as a novel and logical method to exploit the best, by administering anti-cancer treatment at an optimal timing according to circadian rhythms of their anti-cancer action and/or repair mechanism of cancer & normal cells. Understanding of chronobiology and the results of clinical studies back up this new concept. Chronotherapy seems to have all the potential to become tomorrow's accepted, refined oncology practice without adding much to the cost of existing therapy.

INTRODUCTION

Most biological phenomenon show rhythmic relationship that may be diurnal, fortnightly, seasonal or annual and alike. The most frequently observed and easily appreciable is the diurnal (day-night) or 'circadian' rhythm. This circadian rhythm persists and is reasonably uniform in most human including those suffering from cancer, until just before death. The phrase "circadian rhythm" was first described by Halberg and Stephens in 1959[1]

This 'circadian rhythm' might determine the 'best time of day' that can be utilized to treat cancer patient with cytotoxic agent(s), immunotherapy or radiotherapy; though this 'best time' may be quite short (of the range of couple of hours). This fact has been established by extrapolation of preclinical experiments, murine trials and also by multi-armed clinical studies.

MOLECULAR MECHANISM

The biological clock has been found to be represented by the suprachiasmatic nucleus (SCN) which creates biological rhythms under the control of clock genes such as PER1[2,3],

PER2 [2], PER3 [4], CLOCK[5,6], BMAL1[7], TIM[8], CRY1, CRY2[9], tau[10]and coordinates peripheral oscillators for functions including cell proliferation and cellular metabolism.

Cycle duration generated at the SCN is calibrated by the alternation of light/darkness, both directly and through melatonin secretion by the pineal body. Period genes PER and the proteins produced by these genes generate circadian rhythms. The transcription of PER is promoted by the CLOCK/BMAL1 complex, whose activation is inhibited by the PER1/PER2/PER3/CRY1/CRY2/TIM complex. This giant complex acts as a negative auto-feedback system, which has an essential role in generation of circadian oscillation.

This biological clock generates signals of circadian rhythm, which are conducted to the supra-cervical sympathetic nucleus and the pineal body. Generated biological rhythms concern the control of biological functions including those of the autonomic nerve system, endocrine system, and immune system, which are fundamental in homeostasis and in protection against various diseases.

A study suggests that DNA synthesis and repair is intimately linked to circadian rhythm. Since the repair of DNA lesions contributes to the resistance of chemotherapy with DNA damaging agents such as cisplatin, understanding the fundamental molecular mechanism regulating DNA repair pathways is important for cancer therapy[11].

EVIDENCE

Chronomodulated Chemotherapy

Experimental studies in cancer chronotherapy were initially performed by Halberg et al.[12]

Levi's group subsequently undertook many experimental and clinical studies in this field, particularly focusing on chronopharmacology and chronotherapeutics of 5–FU, both alone and in combination with other anti-cancer agents[13, 14,15,16,17]

Hrushesky's group[18, 19] undertook research in chronotherapy for gynecological and genitourinary cancers including advanced renal cell carcinoma. These studies demonstrated the superiority of chronotherapy with respect to response and side effects when compared to conventional chemotherapy.

The work of Giacchetti et al.[20] and Adam et al.[21] has led us to consider cure as a possibility in colorectal cancer patients with liver metastases treated with chronotherapy and surgery. Firstly, a result of lessening side effects, chronomodulated administration has made possible to administer anti-cancer agents in full, effective doses. Secondly, newly developed anti-cancer agents such as 1-OHP have been demonstrated as appropriate for chronotherapy. 1-OHP is a platinum complex compound exhibiting a completely different mechanism of action from Cisplatin.[22]

Phase II study in patients with advanced or recurrent endometrial cancer of any cell type having measurable disease was conducted to determine the effectiveness and toxicity of circadian-timed doxorubicin-cisplatin chemotherapy. Treatment initiated with doxorubicin 60 mg/m^2 over 30 minutes at 6:00 a.m., followed by cisplatin 60 mg/m^2 over 30 minutes at 6:00 p.m. every 28 days and continued for eight cycles or to a maximum tolerable doxorubicin dose of 480 mg/m^2 for patients without progression. Thereafter, responders continued on cisplatin alone. A review of 30 evaluable patients showed 6 (20%) complete responses, 12 (40%) partial responses, and 7 (23%) with stable disease. The number of treatment courses ranged from 2 to 14 with a median of 6.5. The median white blood cell nadir for 27 patients experiencing leucopenia was 1,600/mm^3 (range: 300-3,600/mm^3). For 16

patients experiencing thrombocytopenia the median nadir was 48,500/mm^3 (range: 8,000-138,000/mm^3). The study concluded that circadian-timed delivery of doxorubicin-cisplatin chemotherapy was reasonably well tolerated and demonstrated notable response rates in patients with advanced or recurrent endometrial carcinoma.[23]

Trial in ninety two patients with previously untreated metastatic colorectal cancer was conducted to compare chronomodulated with constant-rate drug delivery. Treatment courses consisted of the daily administration of 5-FU (600 mg/m^2 per day), Folinic acid (FA) (300 mg/m^2 per day), and 1-OHP (20 mg/m^2 per day) for 5 days and were repeated every 21 days (16-day intermission) in ambulatory patients with the use of a programmable in-time pump. Drug delivery was kept constant over a 5-day period in schedule A (47 patients). It was chronomodulated in schedule B (maximum delivery of 5-FU and FA infusions at 0400 hours and maximum delivery of I-OHP at 1600 hours; 45 patients). A risk of partial chemical inactivation of 1-OHP by its 2-hour exposure to the basic pH of the 5-FU solution in the catheter was documented in schedule A. Severe stomatitis (grade 3 or 4 WHO grading system), the dose-limiting toxic effect of 5-FU, was observed in five times as many patients on schedule A than on schedule B (89% versus 18%; $x^2 = 46$; $p < 0.001$). The cumulative dose-limiting toxicity of schedule B was peripheral sensitive neuropathy (WHO grade 2). This side effect was reversible following I-OHP withdrawal. Higher doses of 5-FU were administered in schedule B (median: 700 mg/m^2 per day) compared with schedule A (median: 500 mg/m^2 per day) ($p < 0.0001$; Mann-Whitney *U* test). On schedule B, 24 of 45 patients (53%; 95 percent confidence interval [CI] = 38%–68 percent) exhibited an objective response compared with 15 of 47 patients (32%; 95% CI = 18%–46%) on schedule A ($x^2 = 4.3$; $p = 0.038$). The median progression-free survival was, respectively, 11 and 8 months ($p = 0.19$; log rank). The median survival was 19 months (95% CI = 14.8–23.2) of schedule B and 14.9 months (95% CI = 12.1–17.8) of schedule A ($p = 0.03$; log rank). This study has concluded that chronomodulated drug delivery is both more effective and less toxic.[24]

Another phase III trial using 5-FU, Leucovorin & Oxaliplatin in one hundred and eighty six cases of metastatic colorectal carcinoma comparing 5 days circadian infusion (5-FU + Leucovorin peak 4a.m. and Oxaliplatin peak at 4p.m.) versus flat infusion every 3 weeks also revealed less toxicity in circadian arm, allowing more dose delivery and better response rate.[25]

The efficacy and toxicity of the new anthracycline, 4'-0- tetrahydropyranyl doxorubicin (THP) (50 mg/m^2 intravenous bolus) in association with cisplatin (100 mg/m^2 IV as a 4-hour infusion) was assessed in 31 patients with advanced ovarian carcinoma. Twenty-eight patients were assessable for toxicity among whom, 25 were assessable for response (FIGO stage IIIa, four patients; IIIb, 15 patients; IV, six patients). Nine patients had received prior treatment. Patients were randomized to receive schedule A (THP at 6 hours, then cisplatin from 16 to 20 hours) or schedule B (THP at 18 hours, then cisplatin from 4 to 8 hours). Schedule A was hypothesized as less toxic since THP was best tolerated in the late rest span and cisplatin near the middle of the activity span in experimental studies. The rate of clinical complete response was 52%, that of partial response was 12%, and the overall clinical response rate (CR plus PR) was 64% (schedule A, 73%; schedule B, 57%).

Median progression-free survival and survival times were, respectively, 10 and 19 months. Of 12 patients in clinical CR evaluated at second-look laparotomy, four had a pathological CR (33%), and three had microscopic residual disease. The overall rate of pathological CR was 16%. Schedule A was associated with less neutropenia ($p = 0.10$), thrombocytopenia ($p < 0.01$), anemia ($p < 0.01$), and renal toxicity ($p < 0.05$) than schedule B. Of four patients withdrawn for toxicity, three were on schedule B (one death). Mean dose intensities of THP and cisplatin, respectively, decreased by 30% and 47% over the five initial courses. Such decrease was significantly more pronounced for schedule B than for schedule A in previously untreated patients ($p < 0.01$ from 2-way analysis of variance). Study concluded that THP-cisplatin combination toxicities can be significantly decreased by dosing THP in the early morning and cisplatin in the late afternoon as compared with THP in the evening and cisplatin the next morning.[26]

In a pilot study of chronotherapy, using Cisplatin and 5-FU in sixty patients of Nasopharyngeal carcinoma (NPC), who were randomly designated for induction chrono-chemotherapy plus radiotherapy (CC, 30 patients) or for induction routine-chemotherapy plus radiotherapy (RC, 30 patients); the differences in immediate response, side effects and changes in immunologic parameters between these two groups were analyzed. The chemotherapy regimen of the CC group consisted of cisplatin (DDP) 80 mg/m^2d_1 at 10:00–22:00 h, 5-Flourouracil (5-FU) 750 $mg/m^2/d_{1–3}$ at 22:00–10:00 on the next day and 5-CHO-FH_4 (CF) 200 $mg/m^2/d_{1–3}$ starting at 10:00 h, and repeated every 14 days. The regimen of the RC group was the same as the CC group, with the delivery of cisplatin at a conventional rate and the CF via a continuous 24 h venous injection. The radiotherapy regimen was same in the two groups. Results revealed Complete response rate (CRR) 36.7% vs. 20%, Overall response rate (ORR) 96.7% vs. 73.3%, Myelosuppression grade I,II 43.3% vs. 70% in chronotherapy based treatment and control respectively.[27]

Verma et al compared the efficacy and toxicity of chronomodulated concomitant chemotherapy using weekly Cisplatin at 0600 hour or 1800 hour along with radical external beam radiotherapy (EBRT) in the management of locally advanced head and neck carcinoma (LAHNC). The study concluded that administration of cisplatin; in the evening is better compared to morning administration in terms of disease control and toxicity profile; given concurrent with EBRT, for management of LAHNC.[28]

Now optimal times of administration of more than 20 cytotoxic agents have been proposed for treatment of various cancers and studies are going on. The optimal time has been justified either in terms of better effects or in terms of reduced side effects.[29, 30, 31]

Clinical trials of chronomodulation for many anti-cancer agents are in progress in various malignant diseases, under the control of European Organization for Research and Treatment of Cancer (EORTC).[32]

Chronomodulated Radiotherapy and Immunotherapy

The chronomodulation method has also been tried with radiotherapy and could extend to immunotherapy, the area being underexplored. Only a few studies have addressed the issue.

Shukla et al[33] conducted a randomized prospective trial, in 229 patients to discover any correlation between radiation-related mucositis and the time of radiation. They evaluated the

incidence of grade III/IV mucositis in patients with carcinoma of the cervix treated between 8:00 to 10:00 AM and between 6:00 to 8:00 PM and found that the patients undergoing radiation in the morning showed a significantly higher incidence of grade III and IV mucositis. Also, emphasis was made on theoretical possibility of treating the patients more effectively when the tumor cells are in a radiosensitive phase, with treatment at the same time being less toxic to the surrounding tissues, which are in radio-resistant phase. Marking the time of the day when normal cells and tumor tissues are in different phases is an experimental possibility that could be investigated in studies of cyclin-dependent kinases and other cell cycle marker proteins.

Contrary to this, Bashir et al[34] assessed the incidence of mucositis in patients receiving radiation during morning (before 12:00 noon) and evening (after 4:00 p.m.) hours and the impact of timing of radiation on mucositis in 60 patients of head and neck cancers. Severe mucositis free interval (SMFI) was analyzed. After 3 weeks of treatment, 28.6% patients developed RTOG grade 3 mucositis in the morning group compared to 43.7% in the evening group. SMFI was 33 days (95% CI 22.4, 31.5) for the morning group compared to 22 days (95% CI 31.7, 34.3) for the evening group ($p<0.001$). Study concluded that patients undergoing radiotherapy during the morning hours have less severe oral mucositis and a significantly longer SMFI.

CONCLUSION

Chronotherapy in cancer management may be the future approach considering the feasibility & simplicity of the concept and has shown that existing standard of care may further be explored to extend the benefit without adding cost, especially when infrastructure constraints are there. Both radiation and chemotherapy (may be targeted agents too) can be combined with their best possible administration timings to get better outcomes, in terms of tumor control as well as reduced normal tissue toxicity. The only additional requirement is motivation and compliance.

REFERENCES

1. Halberg F, Stephens AN. Susceptibility to ouabain and physiologic circadian periodicity. Proc Minn Acad Sci. 1959; 27:139-43.
2. Albrecht U, Sun ZS, Eichele G, Lee CC. A differential response of two putative mammalian circadian regulators, mper1 and mper2, to light. Cell. 1997; 91:1055–64.
3. Tei H, Okamura H, Shigeyoshi Y, Fukuhara C, Ozawa K, Hirose M, et al. Circadian oscillation of a mammalian homologue of the Drosophila period gene. Nature. 1997; 389:512–6.
4. Takumi T, Taguchi K, Miyake S, Sakakida Y, Takashima N, Matsubara C, et al. A light independent oscillatory gene mPer3 in mouse SCN and OVLT. EMBO J. 1998; 17:4753-9.
5. Gekakis N, Staknis D, Nguyen HB, Davis FC, Wilsbacher LD, King DP, et al. Role of the CLOCK protein in the mammalian circadian mechanism. Science. 1998; 280:1564-9.
6. King DP, Zhao Y, Sangoram AM, Wilsbacher LD, Tanaka M, Antoch MP, et al. Positional cloning of the mouse circadian clock gene. Cell. 1997; 89:641-53.
7. Ikeda M, Nomura M. cDNA cloning and tissue-specific expression of a novel basic helix–loop–helix/PAS protein (BMAL1) and identification of alternatively spliced variants with alternative translation initiation site usage. Biochem Biophys Res Commun. 1997; 233:258-64.
8. Sangoram AM, Saez L, Antoch MP, Gekakis N, Staknis D, Whiteley A, et al. Mammalian circadian autoregulatory loop: a timeless ortholog and mPER1 interact and negatively regulate CLOCKBMAL1-induced transcription. Neuron. 1998; 21:1101-13.
9. Okamura H, Miyake S, Sumi Y, Yamaguchi S, Yasui A, Muijtjens M, et al. Photic induction of mPer1 and mPer2 in Crydeficient mice lacking a biological clock. Science. 1999; 286:2531–4.

10. Lowrey PL, Shimomura K, Antoch MP, Yamazaks S, Zemenides PD, Ralph MR, et al. Positional systemic cloning and functional characterization of the mammalian circadian mutation tau. Science. 2000; 288:483-92.
11. Kang TH, Lindsey-Boltz LA, Reardon JT, Sancar A. Circadian control of XPA and excision repair of cisplatin-DNA damage by cryptochrome and HERC2 ubiquitin ligase. Proc Natl Acad Sci. 2010; 107(11): 4890-5.
12. Halberg F, Haus E, Cardoso SS, Scheving LE, Kuhl JFW, Shiotsuka R, et al. Toward a chronotherapy of neoplasia: tolerance of treatment depends upon host rhythms. Experimentia. 1973; 29:909–1044.
13. Boughattas NA, Levi F, Fournier C, Lemaigre G, Roulon A, Hecquet B, et al. Circadian rhythm in toxicities and tissue uptake of 1,2–diaminocyclehexane(trans–l) oxalatoplatinum(III) in mice. Cancer Res. 1989;49:3362–8.
14. Levi F, Hrushesky W, Blomquist CH, Lakatua DJ, Haus E, Halberg F, et al. Reduction of cis–diamminedichloroplatinum nephrotoxicity in rats by optimal circadian drug timing. Cancer Res. 1982; 42:950-5.
15. Levi F. Chronobiology in oncology in 1987–1988. Adv Biosci. 1989; 73:261–80.
16. Levi F. Chronopharmacology of anticancer agents. In: Redfern P, Lemmer B, editors. Physiology and pharmacology of biological rhythms. Berlin: Springer; 1997. p. 299–331.
17. Mormont MC, Levi F. Cancer chronotherapy: principles, applications, and perspectives. Cancer. 2003; 97:155–69.
18. Hrushesky WJM, von Roemeling R, Lanning RM, Rabatin JT. Circadian-shaped infusion of floxuridine for progressive metastatic renal cell carcinoma. J Clin Oncol. 1990; 8:1504–13.
19. Kobayashi M, Wood PA, Hrushesky WJM. Circadian chemotherapy for gynecological and genitourinary cancers. Chronobiol Int 2002; 19:237–51.
20. Giacchetti S, Itzhaki M, Gruia G, Adam R, Zidani R, Kunstlinger F, et al. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5–Fluorouracil, leucovorin, oxaliplatin and surgery. Ann Oncol. 1999; 10:663–9.
21. Adam R, Avisar E, Ariche A, Giacchetti S, Azoulay D, Castaing D, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal liver metastases. Ann Surg Oncol. 2001; 8:347–53.
22. Mathé G, Kidani Y, Sekiguchi M, Eriguchi M, Fredj G, Peytavin G, et al. Oxalato-platinum or!-OHP, a third-generation platinum complex: an experimental and clinical appraisal and preliminary comparison with cisplatinum and carboplatinum. Biomed Pharmacother. 1989; 43:237–50.
23. Barrett RJ, Blessing JA, Homesley HD, Twiggs L, Webster KD. Circadian timed combination doxorubicin-cisplatin chemotherapy for advanced endometrial carcinoma. A phase II study of the gynecologic oncology group. Am J Clin Oncol. 1993; 16(6):494-6.
24. Lévi FA, Zidani R, Vannetzel JM, Perpoint B, Focan C, Faggiuolo R, et al. Chronomodulated versus fixed-infusion rate delivery of ambulatory chemotherapy with oxaliplatin, fluorouracil and folinic acid (leucovorin) in patients with colorectal cancer metastases: a randomized multi-institutional trial. J Natl Cancer Inst. 1994; 86(21):1608-17.
25. Levi F, Zidani R, Di Palma M, et al. Improved therapeutic index through ambulatory circadian rhythm delivery of high dose 3-drug chemotherapy in a randomized phase III multicenter trial (abstract). Proc annu Meet Am Soc Clin oncol. 1994; 13:A574.
26. Levi F, Benavides M, Chevelle C, Saunier FL, Bailleul F, Misset JL, et al**.** Chemotherapy of advanced ovarian cancer with 4'-O-tetrahydropyranyl doxorubicin and cisplatin: a randomized phase II trial with an evaluation of circadian timing and dose-intensity. *J Clin Oncol.*1990; 8:705-14.
27. Yang JO, Jin F. A pilot study of chronochemotherapy for nasopharyngeal carcinoma. Chinese Journal of Clinical Oncology. 2006; 3(6):423-7.
28. Verma Y, Chauhan AK, Singh H, Sabharwal R, Bharti M and Kaur P: Chronomodulated chemotherapy and concomitant radiotherapy, for the management of locally advanced, head and neck squamous cell carcinom a. Int J Pharm Sci Res. 2014; 5(3):1015-22.

29. Hrushesky WJM, Bjarnason GA. Circadian cancer therapy. J Clin Oncol. 1993; 11(7):1403-17.
30. Hrushesky WJM, von Roemeling R, Sothern B. Circadian chronotherapy: from animal experiments to human cancer chemotherapy. In: Lemmer B, editor. Chronopharmacology: Cellular and biochemical interactions. New York, Basel: Marcel Dekker, Inc; 1989. 439-73.
31. Bjarnason GA. Chronobiology: Implications for cancer chemotherapy. Acta Oncologica. 1995; 34(5):615-24.
32. Levi F. From circadian rhythms to cancer chronotherapeutics. Chronother Int. 2002; 19:1–19.
33. Shukla P, Gupta D, Bisht SS, Pant MC, Bhatt ML, Gupta R, Srivastava K, Gupta S, Dhawan A, Mishra D, Negi MPS. Circadian variation in radiation-induced intestinal mucositis in patients with cervical carcinoma. Cancer. 2010, 2031-5.
34. Bashir I, Chufal KS, Thakwani A, Bhatnagar A, Alam A, Ghosh D. Prospective study evaluating impact of morning versus evening radiotherapy on mucositis in patients undergoing head and neck intensity-modulated radiotherapy with concurrent chemotherapy. Journal of Young Medical Researchers. Sep-Feb 2014, e1; 1(1):1-7.

How to cite this article:

Chauhan AK, Verma Y, Sabharwal R; Cancer Chronotherapy: The right time to hit! *OncoExpert* 2015:1(1); 1-7