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It's time for chronotherapy!

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Abstract

The EORTC Chronotherapy Group (CTG) stemmed from the International Organisation for Cancer Chronotherapy (IOCC) in 1996. The IOCC was first to initiate large scale multicentre international chronotherapy trials, for the purpose of investigating the relevance of chronomodulated or timed administration of cancer therapy based on biological rhythms. Programmable pumps for cytotoxic chronodelivery and actigraph devices to monitor circadian rhythm alterations linked to cancer were also developed. The unique expertise of the IOCC with regard to cancer chronotherapy furthered its development within the EORTC. The EORTC offers broad expertise in clinical cancer research and opportunities for scientific recognition, intergroup collaborations and translational research. Over the past 5 years, the EORTC CTG has grown from 16 to 48 centres in 12 different countries. It is currently conducting seven multicentre chronotherapy trials which test the relevance of adapting cancer treatment delivery to circadian rhythms. The group aims at developing multiple collaborations to establish a chronotherapy network involving institutions with expertise ranging from experimental chronobiology to new drug testing, disease-specific management and quality of life or survival issues.

Keywords: Chronotherapy; Chronobiology; Circadian rhythms; Chronotolerance; Chronoefficacy

1. Introduction

The Chronotherapy Group (CTG) is a young EORTC group which was created in 1996 as a follow-up to the activities of the International Organisation for Cancer Chronotherapy (IOCC). The clinical studies performed by the IOCC have been internationally acknowledged by the medical community. Under the chairmanship of F. Lévi, who created the Chronotherapy Unit in the Medical Oncology service in Paul Brousse Hospital, Villejuif, France, the IOCC has developed the concept of chronomodulated treatments in cancers. It conducted the first large-scale randomised multicentre international trials of chronotherapy against colorectal malignancies [1–3] and started to extend this treatment method to other tumour types [4–7]. The IOCC has developed, validated and exported a new strategy with curative intent for patients with initially unresectable colorectal cancer metastases, combining effective and well tolerated chronomodulated chemotherapy and surgery of residual metastases [8]. The IOCC has also recognised that patients with cancer could display circadian rhythm alterations that were correlated with poor quality of life and poor survival, independently of all known prognostic factors [9]. Finally, all these trials also required the mastering of programmable drug delivery devices that allowed ambulatory automatic chronomodulated delivery of chemotherapy. The IOCC joined the EORTC and became the Chronotherapy Group of the largest organisation of clinical cancer research in Europe, because both parties felt the timeliness of sharing the unique expertise in cancer patient chronotherapy with the broad spectrum of activities and expertise of EORTC. Indeed, the EORTC constitutes a unique opportunity for scientific recognition, collaborations and translational research.

The aims of the EORTC CTG are to conduct, to develop, to coordinate and to stimulate clinical research for improving the treatment of cancer patients based on biological rhythms and time of drug administration. In order to validate this strategy, the CTG has grown up

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from 15 to 48 centres in 12 countries including Canada, China and USA over the past 5 years. The group has entered 604 patients in five studies (Fig. 1). Two new studies have been open for patient entry during the year 2001. In order to favour communications outside the group, a chronotherapy page has been created on the EORTC web site and can be reached at http://www.eortc.be/home/chrono/

2. Accomplishments

In contrast with most trials where a new drug is being assessed, the trials led by the CTG emphasise testing of the clinical relevance of cancer chronotherapy (Fig. 2). The main goal of the trials aims at validating the concept consisting of the adaptation of cancer treatment delivery to circadian rhythms. A specific statistical design has been developed within the EORTC statistical unit [10] for the so-called 'time finding studies' in order to determine the optimal time window to administer an anticancer agent as a single drug or in combination. Phase III trials compare the 'best' chronomodulated schedule to a conventional delivery scheme in order to contribute in defining new standards of care.

2.1. Protocol EORTC 05962

Infusional 5-fluorouracil (5-FU) with or without cisplatin (CDDP) and with or without chronomodulation against locally-advanced or metastatic pancreatic cancer. A multicentre randomised phase III trial with a 2×2 factorial design: chronomodulation (yes versus no) and CDDP (yes versus no) (F. Lévi and R. Zidani, Study Coordinators). This study is open for patient entry and has recruited 85 patients.

2.2. Protocol EORTC 05963

Multicentre phase III study comparing chronomodulated versus non-chronomodulated first-line delivery of 5-FU, folinic acid and oxaliplatin for metastatic colorectal cancer or loco-regional recurrence upon survival. A multicentre randomised phase III trial (S. Giacchetti, Study Coordinator). This study is open for patient entry and has already recruited 505 patients.

2.3. Protocol EORTC 05971

A multicentre randomised trial, with direct individual benefit, to determine the optimal circadian time of vinorelbine administration combined with chronomodulated infusion of 5-FU in previously treated patients with metastatic breast cancer (B. Coudert, Study Coordinator). This is a multicentre randomised trial of eight groups of 10 patients each, receiving vinorelbine at one of eight dosing times, 3 h apart, in

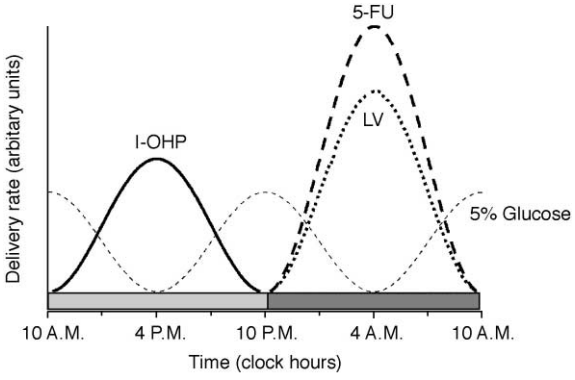

Fig. 2. A typical chronomodulated chemotherapy. LV, leucovorin; l-OHP, oxaliplatin; 5-FU, 5-fluorouracil.

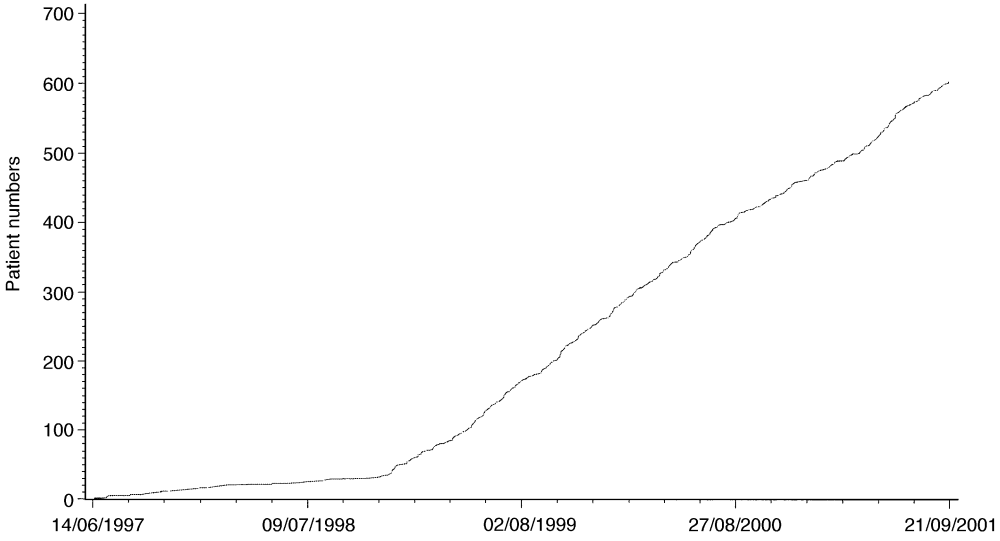

Fig. 1. Chronotherapy Group patient accrual since 1997.

order to define the least toxic time of administration of vinorelbine. This study is open for patient entry and has recruited 41 patients.

2.4. Protocols EORTC 05963 and 05971 Actimetry trials (C. Mormont, C. Focan, B. Coudert, Study Coordinators)

These consist of a multicentre evaluation of circadian system function in patients with colon or breast metastatic cancer. Activity rhythms are regularly and non-invasively measured, during three consecutive 24-h spans, with a small-size wrist-worn piezoelectric accelerometer (Actigraph, Ambulatory Monitoring Inc., New York, USA).

2.5. EORTC protocol 05991

There is a phase II study of chronomodulated preoperative infusional chemoradiation for biliary tract cancer (T. Rich, Study Coordinator). This study has just been open for patient entry and can be implemented in new centres.

2.6. EORTC protocol 05011

This is a time finding study of chronomodulated irinotecan, 5-FU, leucovorin and oxaliplatin as first- or second-line chemotherapy against metastatic colorectal cancer (C. Garufi, Study Coordinator). This study has just been opened for patient entry and can be implemented in new centres.

New studies are in preparation to assess chronotolerance and chronoefficacy of docetaxel and gemcitabine in non-gastrointestinal malignancies [11,12].

Education of the oncological community to chronobiology and chronotherapy principles has been performed through the edition of booklets or reviews by several group members [13–17].

3. Projects

The future of the group will rely on the developing collaborations within a chronotherapy network involving a wide array of teams ranging from experimental chronobiology to quality of life. The CTG has laid the groundworks to develop this concept.

- Experimental research on chronobiology and chronopharmacology is to be developed in INSERM E 0118 unit on cancer chronotherapeutics in Villejuif (F) (Director F. Lévi), in cooperation with INSERM U384 from the Centre J Perrin, in Clermont-Ferrand (F) (P. Chollet) whose research results could provide the basis for future clinical studies [18,19]. Basic investigations on cell cycle-related rhythms in human tissues are to be carried out in the Department of Medical Oncology at Bayview hospital, in Toronto (Can) (G. Bjarnason) and at the Haukeland hospital in Bergen (No) (R. Smaaland). Other basic teams involved in cancer chronotherapeutics.
- Translational research is currently being developed within the group [20–22] and should systematically precede or parallel the clinical studies. Relevance of circadian rhythms for quality of life will be assessed more systematically in phase III trials along with circadian biological parameters [23–25].
- Chronoevaluation should be introduced in the very early development of drug. This will be done in close cooperation with the EORTC ECSG/NDDG in order to propose two types of strategies. A drug salvage chronomodulation project could be offered for those drugs with excessive toxicity precluding further preclinical or clinical development in order to determine whether a chronomodulation of the drug could reduce toxicity. An efficacy and toxicity chronomodulation project could also be implemented in order to increase the efficacy/toxicity ratio of a new compound.
- Intergroup collaboration within EORTC has grown rapidly especially with the Quality Assurance Group (A. Marinus) and the Quality of Life Group (A. Bottomley). Special contacts are kept with several EORTC clinical groups in order to share studies. The National Cancer Institute (NCI) and the National Cancer Institute of Canada (NCIC) will also be associated with the future developments in chronotherapy.
- Economics aspects of cancer chronotherapy will also be studied to demonstrate the feasibility and economy of the chronotherapeutic procedures [26].

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