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Cancer chronotherapeutics

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The cytotoxicity of over 30 anticancer drugs vary by 50% or more as a function of dosing time along the 24-h time scale in laboratory rodents. Mechanisms involve circadian changes in cellular metabolism and proliferation processes, as well as drug pharmacokinetics. Moreover, the administration of chemotherapy at the least toxic time usually achieves best antitumor efficacy in experimental tumor models.

The coupling of several chronopharmacology mechanisms with the rest-activity cycle both in mice and in patients led to the design of chronomodulated infusions adapted to circadian rhythms (chronotherapy). Thus, the activity of dehydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme of 5-fluorouracil (5-FU) catabolism, was ~ 3 to 6 fold larger in liver and bone marrow in the first half of the rest span as compared to the middle of the active span of mice or rats. Similarly DPD in human circulating mononuclear cells was ~ 40% larger at 1:00 at night as compared to midday. High DPD coïncided with lowest proportions of cells undergoing DNA synthesis in bone marrow, gut, oral mucosa and skin. This resulted in a better tolerability of 5-FU in the early rest span. Conversely, reduced glutathione (GSH) also displayed a circadian pattern in liver and gut. Highest levels were found during the activity span in rodents and accounted for the better tolerability of platinum complexes near this circadian time (reviewed in Lévi, 1997).

Chronotherapy has been implemented in 1500 patients with metastatic colorectal cancer receiving 5-FU and leucovorin (LV), with or without oxaliplatin (l-OHP) (Lévi, 1996).

Sinusoïdal chronomodulated delivery of 2- or 3-drug chemotherapy was performed in the patient's home or during its usual activities, with a computer-programmed multi-reservoir pump (IntelliJect, Aguettant, Lyon, France). Courses lasted 4-5 days (d) and were repeated every 14-21d.

Drug	Infusion times *(clock hours)*	Peak delivery time *(clock hour)*	Daily dose *(mg/m²)*
5-FU	22:15 to 09:45	4:00	700 - 1200
LV	22:15 to 09:45	4:00	300
l-OHP	10:15 to 21:45	16:00	25

In 2 multicenter randomized trials involving a total of 278 patients with metastatic colorectal cancer, 3-drug chronotherapy proved largely superior to flat infusion with respect to both tolerability and antitumor efficacy (Lévi et al., 1997) :

Effect	Flat	Chrono	p
Hospitalization for tox.	31*	10	*0·001*
Severe mucositis	76	14	*0·0001*
Functional impairment (periph. sensory neuro.)	31	16	*0·01*
Tumor response > 50%	29	51	*0·003*

*Percentage of patients

The better tolerability of chronotherapy further allowed an increment of both 5-FU and l-OHP doses, which in turn further improved objective tumor response rate to 66%. This allowed to surgically remove previously unoperable metastases and achieve >20% survival at 3 years. Conventional regimens produce ~ 20% objective responses and < 5% 3 yr survival.

Second generation programmable-in-time pumps have simplified chronotherapy administration and decreased its cost. A broad use of fully ambulatory chronotherapy requires thorough definitions of drug stability, compatibility with pump reservoirs and admixtures with other medications (including antiemetics, analgesics...).

The relevance of chronotherapy to improve tolerability and quality of life is now investigated for vinorelbine and irinotecan. For this purpose, randomized trials involve the administration of « standard » drug doses in patients with breast or colorectal cancer. The European Organization for Research and Treatment of Cancer is now assessing whether chronotherapy improves survival as compared to conventional delivery of chemotherapy in patients with colorectal cancer. For this purpose, maximum tolerated doses are given in each respective arm.

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