A. Introduction

Several strategies are aimed at increasing the selectivity of anticancer agents against cancer cells. Some are based on tumor cell biology: new drug development, resistance revertants, etc. Others are targeted at host cells: development of analogs with less toxicity than the parent drug, combinations of cytostatics without additive toxicities, scheduling and/or supportive care in order to increase chemotherapy tolerability, etc. (De Vita et al. 1993). A dose-efficacy relationship has been repeatedly established for cancer chemotherapy (Hryniuk 1988). For this reason, the chronobiology of normal cells has constituted the main basis for attempting to improve the therapeutic index of cytostatic drugs. It was expected that an increase in drug doses, and therefore therapeutic efficacy, would result from an adaptation of drug delivery to circadian rhythms (chronotherapy). We will examine the several steps which have led to the validation of the clinical relevance of chronotherapy in medical oncology that was anticipated more than 20 years ago (Haus et al. 1972; Halberg et al. 1973). Only the circadian aspects will be considered.

B. Experimental Chronopharmacology

I. Toxicity Rhythms

Circadian dosing time influences the extent of toxicity of ~30 anticancer drugs, including cytostatics and cytokines, in mice and rats (Lévi et al. 1988a, 1994a; Mormont et al. 1989; Perpoint et al. 1995). The methodology that was mostly used to demonstrate this phenomenon firstly consisted of the administration of the same drug dose to different groups of animals, each group corresponding to a different circadian stage. Six circadian stages, usually located 4 h apart, have commonly been used. Time has usually been expressed in hours after light onset (HALO). Nocturnally active mice or rats have mostly been synchronized for 1–3 weeks with an alternation of 12 h light (L) and 12 h darkness (D) (LD 12:12). A 3-week span appears a safe period for biological rhythms to adjust to a synchronization regimen differing by 8 h or more from the previous one. Other photoperiodic schemes have occasionally been used: natural LD, which varies according to the season and latitude; artificial LD 8:16 (so-called...
winter photoperiod); or LD 16:8 (so-called summer photoperiod). Autonomous chronobiologic facilities have largely improved the feasibility of chronopharmacologic experiments since they allow for any endogenous circadian stage to be explored at any desired local time. For all these drugs, survival rate varies by 50% or more according to circadian dosing time of a potentially lethal dose. Such large differences are observed irrespective of injection route – intravenous or intraperitoneal – or number of injections – single or repeated (Figs. 1,2).

Pirarubicin, an anthracycline compound, mostly exerts myelosuppressive effects, which are lowest following dosing in the second half of the diurnal rest span (~7 HALO) (Lévi et al. 1985). Mitoxantrone, an anthracycline-related compound, displays lowest hematologic toxicity 8 h later (15 HALO) (Lévi et al. 1994b). Platinum complex analogs – cisplatin (cis dichlorodiamineplatinum, CDDP), carboplatin (cyclobutane dicarboxylatoplatinum II, CBDCA) and oxaliplatin [oxalato (2-)0,0' platinum] (L-OHP) – are also best tolerated near the middle of the nocturnal activity span of mice and rats, despite the differing target tissues of toxicity of these compounds: CDDP is mostly toxic to both kidney and bone marrow, CBDCA to bone marrow and colon mucosa and L-OHP to jejunal mucosa and bone marrow (Hrushesky et al. 1982a; Lévi et al. 1982a; Boughattas et al. 1988, 1989, 1990). Two fluoropyrimidines – 5-fluorouracil (5-FU) and floxuridine (FUDR) – are antimetabolites which dis-

![Diagram](image_url)

**Fig. 1.** Circadian change in tolerability of anticancer agents in mice or rats. End point is survival following a potentially lethal dose at one of six dosing times, 4 h apart. Animals are synchronized with an alternation of 12 h light (L) and 12 h darkness (D) (LD 12:12). Time is expressed in hours after light onset (HALO), since light onset is the main signal which resets the circadian cycle in these nocturnally active animals. The least toxic time, usually by 50% or more, is indicated with an arrow for the corresponding agent(s). (Modified from Lévi et al. 1988)