Systems Approaches to Personalize Cancer Chronotherapy

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Background

Among the therapeutics strategies that have proven a benefit for cancer patients in the past decades, **cancer chronotherapy**- that is adjusting drug delivery to the circadian timing system (CTS) which rhythmically regulates the organism over the 24-h span- is considered as very promising [1]. Indeed, clinical trials have shown that proper chemotherapy timing decreases anticancer drug toxicities by up to 5-fold and nearly doubles their antitumor efficacy [2, 3]. Circadian timing is especially relevant for anticancer drugs, which are often utilized at maximal tolerated doses and responsible for severe toxicities. Thus, a current clinical challenge lays in reducing their life-threatening and dose-limiting side effects.

It is now demonstrated that the patient's chronotype, sex and genetic background influence both the potential benefit of chronotherapy compared to non-circadian based treatments, and the optimal drug timing for each individual. Recently available circadian biomarkers assessment has revealed up to 12 h inter-patient differences regarding the timing of midsleep and the circadian maxima of skin surface temperature or physical activity [1]. Further, the administration of the same chronomodulated schedule to patients with metastatic colorectal cancers achieved an increase in the survival of men and a slight decrease in that of women compared to conventional administration [2]. These recent findings advocate for personalized chronotherapeutics, which requires the design of specific chrono-infusion schemes for each patient or patient subgroup [1]. Such clinical challenge may highly benefit from Quantitative Systems Pharmacology (QSP) frameworks that need to integrate the patient-specific temporal features of healthy and tumour tissues.

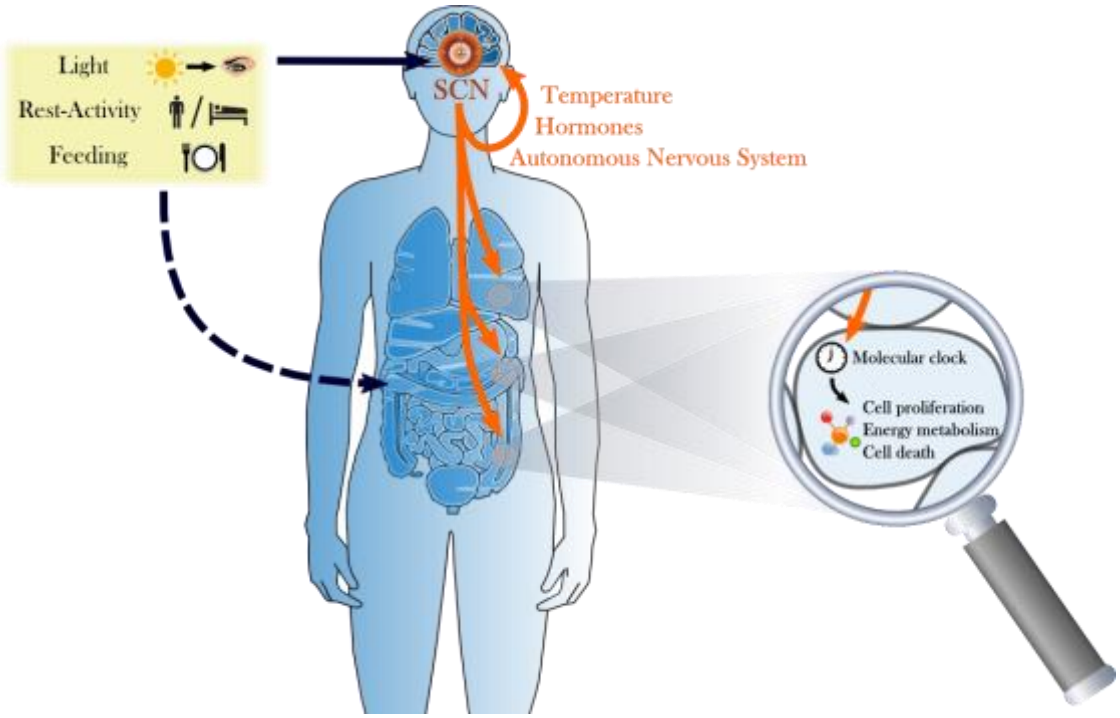

Figure 1: The Circadian Timing System, *see part II A. of [1] for details*

The circadian timing system (CTS) rhythmically controls the organism on the 24h span. It is composed of a central pacemaker located in the brain that generates rhythmic physiological signals controlling the autonomous molecular circadian clock present in each nucleated cell (Figure 1, see part II A. of [1] for details). This circadian organization induces daily variations in drug pharmacokinetics-pharmacodynamics (PK-PD) and cytotoxicity. Over 40 anticancer agents displayed circadian rhythms in their toxicity -or chronotoxicity-and 28 compounds demonstrate variations in their antitumor activity- that is chronoefficacy (Figure 2). Interestingly, best antitumor efficacy of single agent or combination chemotherapy usually corresponds to the delivery of anticancer drugs near their respective times of best tolerability in rodent studies [1].

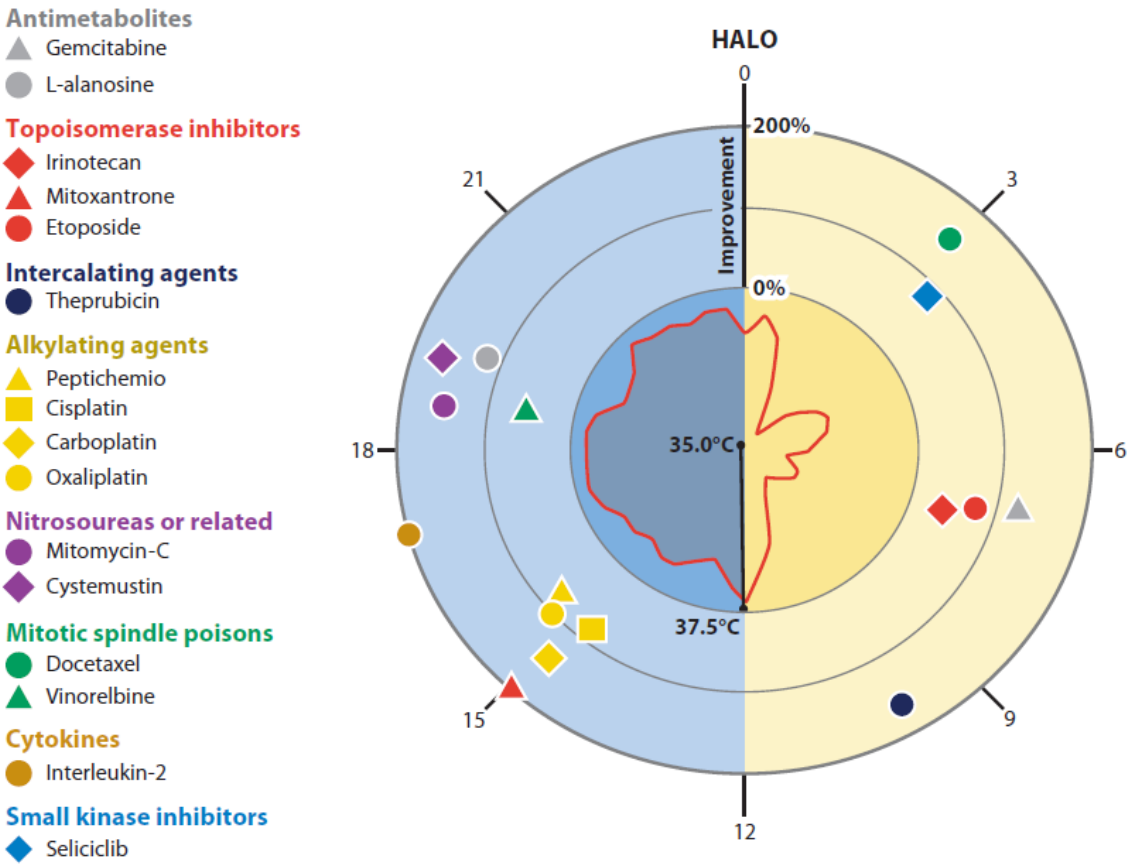

Figure 2 : Anticancer drug chronotoxicity*. Circadian timing associated with best tolerability, in HALO (hours after light onset, ranging from 0 to 24) and relative magnitude of survival benefit from optimal to worst timing, ranging from 0 to 200%. The diagram illustrates chronotolerance for 16 anticancer drugs studied in male B6D2F1 mice, synchronized with LD12:12. The average circadian rhythm in body temperature is shown in the internal circle and provides a CTS biomarker, an endogenous reference for optimal drug timing.*

The decrease in treatment toxicities arising from treatment chronomodulation may then be explained by different molecular status of healthy cells over the 24h span protecting them from the drug effect at particular times of the day. Whereas normal cells usually display well-synchronized circadian variations within a tissue, tumor cells often present disrupted circadian rhythms, which has become a hallmark of cancer. This escape from the circadian control allows for increased proliferation [2] and may be associated with a decreased sensitivity to anticancer drugs [1]. The circadian pattern of efficacy shown in preclinical and clinical studies may then arise from i) the host CTS which rhythmically controls drug systemic concentration and tumor

uptake and ii) the circadian drug effect on the cancer cells' molecular clock and intracellular chronoPK-PD [2].

Further, anticancer drugs may themselves disrupt the CTS in particular by perturbing clock gene expression at the intracellular level. As chronotherapy relies on strong circadian rhythms in healthy tissues, efforts must be made to minimize clock disruption that includes proper circadian timing and possible co-administration of cytotoxic drugs with chronobiotics and/or targeted agents (see part VIII.B. of [1]).

Questions to explore:

1) What are the necessary conditions to ensure a benefit of chronotherapy compared to standard of care? What type of pharmacological interventions could increase it?

Data available:

- Conditions on the drugs themselves (range of half-life, specific PK or PD mechanisms…) may be investigated. Classical PK compartment-based and Emax PD models could be supplemented with circadian rhythms to draw conclusions on the necessary conditions to obtain chronoPK or PD effects. A more elaborated model of irinotecan cellular chronoPK-PD may also be used [4, 5].
- Second, conditions on the CTS of the patient are probably determinant for obtaining a benefit of chronotherapy. What circadian rhythms have the most determinant effects on chronotoxicity/efficacy? Candidates would be: central pacemaker in the brain (suprachiasmatic Nucleai), signals to peripheral organs (temperature, cortisol,…), cell-to-cell tissue synchronization, and intracellular clocks. Several tissues may be investigated including the liver (drug metabolism), the intestine and bone marrow (drug toxicities), and the tumor (drug efficacy). Further, what interventions and at which level would be the most likely to increase chronotoxicity/chronoefficacy amplitude rhythms, hence potential benefit of chronotherapy?

2) How can we explain the fact that circadian times of least toxicities usually coincides with that of highest antitumor efficacy?

Data available:

A striking coincidence characterizes the circadian time of best tolerability and that of best efficacy for most chemotherapy drugs in rodents. Such observation also applies to combination chemotherapy involving two or more anticancer drugs: indeed, the best efficacy of the combination treatment is achieved when each drug is administered at its own circadian time of best tolerability, as shown for docetaxel-doxorubucin, for irinotecan-oxaliplatin, and for gemcitabine-cisplatin in tumor-bearing mice [1]. These results support tight mechanistic links between chronotolerance and chronoefficacy.

A working hypothesis is that the time of best tolerability is also the time of minimum drug-induced CTS disruption, thus ensuring a control of the CTS on tumor growth that acts synergistically with the anticancer drugs. Indeed, CTS disruption may allow for a more favourable environment for cancer cells. In particular, the immune response may be altered by disruption of cell synchronization at the level of the tissue or/and organ synchrony at the whole-body scale.

References

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