ANCTHE IMPORTANCE OF CHRONOBIOLOGY IN THE TREATMENT OF HEMATOLOGICAL MALIGNIES.

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Chronobiology is the cantitative study of the temporal relationships of biologic phenomena.
Biophisical and biochemical processes vary with respect to time in a regular and predictible periodic manner across several rythmic frecvencies. Endogenous biological ritms have been demonstrated at all biological levels, from yeasts and nucleated unicells to man and at all levels of biological organization.
The existence of molecular time-keeping mecanism, „clock" gene was first inferred for Drosophila melanogaster which has been named per (period).
There is evidence to suggest that suprachiasmatic nucleus (SCN) of the hypothalamus is a site of critically important circadian pacemaker cells in mammals.
The protooncogene C-fos may be a molecular component of photic pathway necessary for entrainment of mammals to the light/dark cycle.
At least three major biologic rytms have been defined.
- The circadian rhytm (20-28h) the solar day
- The circatrigintan rhytm (30±7 days), the lunar month
- The circannual rythm (12±2 months), the year.

The basic properties of biological rythms are similar in plants and animals.
The rhytms are endogenous and genetic in origin, persist without time clues and are regularly influenced by cyclic variations of certain environmental factors called syncronizers.
Under constant conditions the endogenous circadian period lenghts of the various species are not precisely 24h (more than 24h, but less than 25h).
If their circadian pace makers were not reset by the daily schedule, the timing of their endogenous rhytms would be delayed with respect to clock time each day.
In man and many other species the most powerfull synchronizers of the circadian rhytms are the diurnal alteration of lyght (activity) and darkness (rest) and our 24-h life routine.
There are two general categories of circadian organization wich bear most directly upon the practice of oncology:
- the circadian aspects of drug handling
- circadian organization of cell division in normal and malignant tissues

1. Pharmacokinetics of many anticancer drugs show a circadian temporal variation depending on the time of their administration.
The temporal variations that have been documented in drug absorbtion and distrubtion, metabolism and excretion could explain this to a large extent.
Hemodinamic circadian ritms are also potentially relevant to drug delivery and metabolism.
Hepatic blood flow have a significant circadian variation with the maximum at 8 a.m.
This would affect the metabolism of drugs, that exhibit hepatic blood flow dependent clearence.
Tumor blood flow and therefore drug delivery are two fold higher during daily activity span of nocturnally active rats.
2. Most normal tissues are either more or less sensitive to effects of drugs at specific times of day.
The variable sensitivity can be explained and quantified in terms of bioperiodic changes in the concentration of receptors of a given sistem for a given drug.
In other cases, a circadian variation of cellular defense mecanisms may play a part.
Cell proliferation rytms in the gastrointestinal tracts and bone marrow are relevant to the oncologist since these are common targets for toxicity of antineoplastic agents.
In the gastrointestinal tract the highest DNA syntethic activity is between 5-9 a.m. each morning.
In bone marrow are blood cells undergoes strong regular temporal variations – circadian and seasonal.
The percentage of cells in DNA syntesis in the bone marrow presents a large variation along the circadian time scale for each 24h profile 29 to 339% with the highest DNA syntetic activity between 7 a.m. and 4 p.m.
Two clinical trials have demonstrated an asinchrony in DNA syntesis between tumor tissue and normal tissue.
In nonHodgkin's lymphoma the within day variation in S-phase values observed in individual patients ranged from 21 to 353% and the majority of peak values were found late in the evening or during the night.
This peak is 12h out of phase with the circadian variation in S-phase in normal bone marrow.
The avaiability of portable infusion pumps capable of delivering single or multiple drugs each with their optimal circadian scheduling has made thechnical application and testing of these principles plausible.
Clinical benefit of this strategy depends upon a certain cytokinetic and metabolic asynchrony between the circadian susceptibility patterns of the normal tissues at risk for drug toxicity and the tumor.
If this asynchrony exist then at the time when the normal tissue are less vulnerable to the toxic effect of a drug, the tumor may not be protected to the same extent.
This would allow more dose intensive treatment to be given without increased toxicity.
A similar argument can be made for the toxic biological response modifiers (IL2, TNF, IFN). Whereas those that are nontoxic (EPO, G-CSF) might achieve a better therapeutic effect with a lower and less costly dose if given at the optimal time