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Cancer treatment: A step towards personalized chronotherapy

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Cancer chronotherapy consists in administering treatment at an optimal time. Because the body is governed by precise biological rhythms, the efficacy of anti-cancer drugs can be doubled and their toxicity reduced five-fold depending on the exact timing of their administration. However, important differences in biorhythms exist between individuals, which chronotherapy has not been able to take into account until now. An international study conducted on mice and coordinated by researchers from Inserm, CNRS and Universit Paris-Sud has paved the way towards personalized chronotherapy treatments. In an article published in the journal *Cancer Research*, the team has shown that the timing of optimal tolerance to irinotecan, a widely used anti-cancer drug, varies by 8 hours depending on the sex and genetic background of mice. They then developed a mathematical model that makes it possible to predict, for each animal, the optimal timing for administering the drug. They now hope to test this model on other drugs used in chemotherapy.

The body's metabolism follows a 24 hour rhythm, driven by the circadian clock. Consequently, at certain precise times of the day or night, a given drug may prove to be more toxic to cancer cells and less aggressive to healthy cells. Cancer chronotherapy, discovered some twenty years ago by Francis Lvi, seeks to improve the efficacy of chemotherapy treatments. His research has shown that this efficacy can be doubled, depending on the time at which they are administered. Furthermore, it is precisely at this optimal time that the drugs prove to be five times less toxic to the body.

However, research points to the need for personalizing chronotherapy. Indeed, biorhythms can change from one person to the next. For example, although the optimal timing is the same for 50% of patients, the remaining 50% are either ahead of or behind this time. The team headed by Lvi wanted to elucidate the factors that affect these differences in biorhythms.

To do this, the researchers studied the toxicity of irinotecan, an anti-cancer drug widely used in the treatment of cancer of the colon and pancreas, as a function of the timing of its administration in four strains of male and female mice. For the first time, they were thus able to observe that the time of best tolerance to treatment varied by up to eight hours from one group of rodents to the next, depending on their sex and genetic background.

The researchers then worked on developing a method able to predict this optimal drug timing independently of sex and genetic background. To do this, they measured the expression of 27 genes in the liver and colon over 24 hours and then analyzed these measurements using a methodology derived from systems biology. In this way, the researchers were able to construct and validate a mathematical model to precisely predict the timing at which irinotecan is less toxic to the body using the expression curve of two genes, known as Rev-erb and Bmal1, which regulate the metabolism and proliferation of cells.

The researchers are now aiming to validate this model on other drugs used in chemotherapy. In addition to gene expression, they would also like to find other physiological parameters related to the biological clock that could help predict the optimal timing of treatments for each patient. This work should make it possible to enhance the efficacy and tolerance of such treatments as well as considerably improve the quality of life of patients.

More information: A circadian clock transcription model for the personalization of cancer chronotherapy. Li XM, Mohammad-Djafari et al. *Cancer Research*. First published online on 23 October 2013. DOI: 10.1158/0008-5472.CAN-13-1528