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The Norton–Simon hypothesis: designing more effective and less toxic chemotherapeutic regimens

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Successful treatment of bacterial infections is largely a result of our ability to exploit the biochemical differences between bacteria and human cells so as to achieve toxic drug concentrations in the former while sparing the latter. Unfortunately, such high selectivity is at present elusive in the chemotherapy of human cancers. Hence, great effort is required to determine dose schedules that maximize the benefit/toxicity ratio, particularly for multiple agent regimens.

Extensive clinical experience has taught us that trial-and-error, in the absence of guiding principles, is inefficient in this regard. Seeking guiding principles, we used clinical and laboratory observations to derive a phenomenological law relating the effect of cytotoxic chemotherapy on tumor size to the growth dynamics of the tumor. This relationship was referred to by others as the Norton–Simon hypothesis, i.e. that chemotherapy results in a rate of regression in tumor volume that is proportional to the rate of growth for an unperturbed tumor of that size.[1–3] This relationship differed from the existing "log kill" model, which stated that a given dose of chemotherapy killed the same fraction of tumor cells, regardless of the size of the tumor at the time of administration.[4] The log kill model worked for experimental leukemia because the growth dynamics of the cancer were constant during the course of observation, but it failed when applied to human and experimental solid tumors in which tumor size approached a plateau level, dynamics that were often adequately captured by Gompertzian growth curves.[5]

The mathematical conclusion of our analysis is that a tumor's size at a given time point depends on the integrated drug effect during the course of treatment up to that time (To view this equation refer to the supplementary information on the *Nature Clinical Practice Oncology* website). The drug effect is not just the pharmacokineticists' concentration multiplied by time, because the relationship between drug dose level (and hence concentration) and anticancer effect is not always linear. For a given integrated drug effect, the chance of eradicating the tumor is maximized by delivering the most effective dose level of drug over as short a time as possible. Thereby, tumors given less time to grow between treatments are more likely to be eradicated. Administering high quantities of the drug at the beginning of the chemotherapy cycle (i.e. front-loading) might fail for two reasons. First, levels higher than a certain concentration may not increase the killing of cancer cells. Second, even if they did, the toxicity could be intolerable. In practice, optimizing the schedule means determining a way to give the maximum integrated effect over as short a time as possible, consistent with reasonable quality of life.

The situation is more complicated when considering the combination of different chemotherapy regimens. Bonadonna *et al.*[6] compared alternating and sequential dose schedules of adjuvant cyclophosphamide, methrotrexate, and fluorouracil (CMF) given simultaneously in combination with doxorubicin (A) for patients with high-risk stage II breast cancer. A sequential regimen consisting of 4 courses of doxorubicin followed by 8 courses of CMF ($A^4 \rightarrow CMF^8$) resulted in superior long-term disease-free and overall survival compared with an alternating regimen of two courses of CMF followed by one course of doxorubicin, repeated for four cycles ($[CMF^2 \rightarrow A] \times 4$).[7] The dose levels, interval lengths, and total treatment duration were identical in both arms. The alternating schedule was predicted by the Goldie–Coldman hypothesis to decrease the development of mutations that were resistant to all of the drugs.[8] As predicted by the Norton–Simon hypothesis, the sequential regimen was superior because the integrated drug effects are greater, i.e. four consecutive administrations takes less time, and is therefore more 'dose-dense', than an alternating approach. This is especially relevant to these regimens because of the reasonable assumption that the cell kill per course of chemotherapy is greater for doxorubicin than for CMF.[7]

In the North American Inter-Group factorial trial design (CALGB 9741) the concept of dose-dense adjuvant chemotherapy was further tested in patients with node-positive breast cancer.[9] Investigators asked if dose-dense 2-week inter-treatment intervals (supported by the use of granulocyte-colony stimulating factor) were better than the conventional 3-week intervals. The trial also investigated whether doxorubicin, cyclophosphamide and paclitaxel (T) used in combination $(AC)^4 \rightarrow T^4$ were better than a single-agent sequence ($A^4 \rightarrow T^4 \rightarrow C^4$). The Norton–Simon hypothesis correctly predicted that the dose-dense schedule would be superior to the standard schedule for either regimen, with observed reductions in the annual odds of disease recurrence by 26% and the annual odds of death by 31%.[9] Both effects were statistically significant ($P = 0.01$), although follow-up is continuing.[9] Our model also predicted that, for a given dose density, there would probably be no difference between the concurrent and sequential use of cyclophosphamide. The dose densities of both doxorubicin and paclitaxel are identical for the two regimens at all times, because both involve administration of four courses of A followed by four courses of T. The dose density of cyclophosphamide is greater in the $(AC)^4 \rightarrow T^4$ regimen, because this drug is administered sooner compared with the sequential regimen, but whatever small differences in efficacy that might accrue from this would have to be seen in the context of the greater activity of doxorubicin and paclitaxel. Hence, it is not surprising that no differences in clinical outcomes were observed between $(AC)^4 \rightarrow T^4$ and ($A^4 \rightarrow T^4 \rightarrow C^4$) in the clinical trial.[9]

A clinical trial reported by Venturini *et al.*[10] compared six cycles of fluorouracil, epirubicin and cyclophosphamide administered every 3 weeks or every 2 weeks with filgastim support in a very heterogeneous group of patients with primary breast cancer. Although the overall difference in outcomes was not statistically significant, the power was limited and the dose-dense regimen seemed substantially more effective than the control regimen for patients expected to be sensitive to anthracycline chemotherapy, i.e. those with one of the following characteristics: young age, negative hormone receptor status, high tumor proliferative rate or HER2 positivity.

While the term 'dose dense' might suggest greater toxicity, results demonstrated that the 2-weekly regimens caused fewer neutropenic complications and, in general, no greater toxicity, except for easily managed anemia and bone pain, compared with the longer schedule.[9] Most new molecularly-targeted drugs are not so specific for tumor cells that optimal scheduling is insignificant. Consequently, it will remain imperative to use mathematical methods to guide clinical trial design. The consequences of 'rugged empiricism' are great; it would slow progress and cost too much in human as well as economic terms to be an acceptable alternative. The approach we have used and advocate applies a phenomenological theory based on empirical observations from both laboratory and clinic. That it has so far proven useful for the design of more effective and less toxic chemotherapeutic regimens should encourage further explorations of this type.[11,12]

Supplementary information is available on the *Nature Clinical Practice Oncology* website.

Competing interests
The authors declared they have no competing interests.

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