Schedule-Dependence in Cancer Therapy: What is the True Scenario for Vitamin C?

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Abstract

Schedule-Dependence is a very common phenomenon that is observed with drugs used for cancer therapy. Large intermittent doses are often more toxic and less effective than smaller repeated doses. The state of the art in schedule-dependence and its potential role for designing the optimal vitamin C dosing regimen is discussed in the light of some literature reports and preliminary results from a pilot study we conducted at high vitamin C dosage. Accordingly, we recommend that any further clinical protocol for pharmacokinetic assessment of vitamin C in cancer patients should be conducted based upon the schedule-dependence approach.

Key words: Schedule-dependence, vitamin C, cancer therapy, pharmacokinetics.

Background

Many agents in antineoplastic chemotherapy are highly schedule dependent. The axiom underlying this pattern is: "Response is NOT proportional to cumulative drug dose or area under the disposition curve (AUC), instead response is proportional to cumulative drug effect" (i.e. same total dose size but different response depending on dosing schedule). For instance, fewer administrations of larger doses of cisplatin and etoposide, both widely used as antineoplastic chemotherapeutic agents, were generally less satisfactory than multiple but smaller treatments. The most effective sequence was an alternating regimen, by which the cytoreductive effects of cisplatin resulted in recruitment of quiescent cells into active proliferation, enhancing in turn the efficiency of subsequent etoposide treatment.[1]

Erttmann et al. studied the serum doxorubicin elimination kinetics after dosing this drug following different dosage schedules: 30 mg/m^2, 50 mg/m^2, and 4x15 mg/m^2 every 10 h by bolus injection to few cancer patients.[2] The results obtained by these authors provided strong evidence for a nonlinear dependence of doxorubicin serum elimination on the dose and administration schedule used. Comparing the 15 and 30 mg/m^2 dose there was no significant increase in early drug levels but a marked increase in terminal half-life. At doses higher than 30 mg/m^2, however, there was a steep increase in early drug levels, too. Moreover a marked accumulation of the anthracycline in the central compartment following short-term (4x15 mg/m^2 every 10 h) consecutive administration was found. Accordingly, the authors concluded that in order to obtain an optimal concentration x time product by single bolus injection a dose equal to or higher than 30 mg/m^2 should be used. However, in this dose range a steep dose-dependent rise in early drug levels is to be expected. As early high serum levels correlate with congestive heart failure, administration schedules reaching effective concentration x time products without high peak levels such as continuous infusion or consecutive administration of low doses seem to be necessary.[2]

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In another study the authors aimed at determining possible schedule dependent pharmacokinetic and pharmacodynamic interactions between gemcitabine (2, 2-difluorodeoxycytidine, dFdC, given as 30-min infusion, 800 mg/m^2) and cisplatin (cis-diamminedichloroplatinum, CDDP, given as one-hour infusion, 50 mg/m^2) in 33 patients with advanced stage solid tumors in a phase I trial. Sixteen patients had a four-hour interval between gemcitabine (days 1, 8, 15) and cisplatin (days 1 and 8), followed by the reverse schedule and 17 patients had a 24-hour interval between gemcitabine (days 1, 8, 15) and cisplatin (days 2 and 9), followed by the reverse schedule. Of all schedules the treatment of patients with cisplatin 24 hours before gemcitabine led to the highest dFdCTP (gemcitabine–triphosphate) accumulation and total platinum levels in plasma. These characteristics formed the basis for further investigation of this schedule in a phase II clinical study.[3]

Likewise, Zimmerman and co-workers found a schedule dependence in the antitumoral activity, as well as the toxicity, of polyethylene glycol-interleukin 2 (PEG-IL-2) upon comparison to that of recombinant human IL-2 in three transplantable syngeneic murine tumor models (Meth A fibrosarcoma, B16 melanoma, and Pan-02 pancreatic carcinoma). According to the authors, the efficacy of PEG-IL-2 was dose dependent and was greatest on a q7d x 2 schedule in Meth A and B16.[4] But, when the same total doses were further divided and delivered on any of several alternative schedules, either the efficacy was reduced or the toxicity of the treatments was increased. In Pan-02, a recombinant human IL-2-resistant tumor, PEG-IL-2 treatment on either the q7d x 2, q4d x 3, or q3d x 4 schedule resulted in approximately a 200% increase in lifespan; however, the toxicity of the treatment increased as the interval between doses was shortened. After simulating the corresponding pharmacokinetic profiles of these various regimens the authors hypothesized that the observed schedule dependence is also affected by the kinetics of the host's biological response to IL-2.[4]

Notably, Hill and colleagues investigated the effects of multiple daily or twice daily dosing with combretastatin A4 phosphate (CA4P, tubulin depolymerizing drug that selectively disrupts tumor-associated vasculature) on the vascular function, cell survival and growth of syngeneic and spontaneous breast cancers in mice.[5] In both transplanted and spontaneous tumors significant growth retardation is observed if CA4P is administered daily (10 doses x 50 mg/kg), whereas no significant effects are seen if the same total dose (500 mg/kg) is administered as a single bolus injection. Further investigation of dose scheduling showed that the initial antivascular effects of CA4P are enhanced by administering the drug in 2 equal doses separated between 2 and 6 h. The twice daily dosing schedule (25 mg/kg twice a day) produced increased growth retardation compared to the 50 mg/kg once a day schedule in the transplanted CaNT tumor. These studies indicated that the potential anti-tumor activity of CA4P when used as a single agent in clinical trials may be enhanced when used in multiple dose schedules.[5]

Some authors suggest that, after a kinetic analysis of the tumor cell-killing drug effect, a cell cycle phase-specific and time-dependent action can be demonstrated, which provides a reasonable explanation for the schedule-dependent therapeutic effect of such anti-tumor drugs. As an example, the inhibitors of enzyme topoisomerase I (i.e., camptothecin analogues) appear to be toxic only in S phase cells, and in vitro cytotoxicity is considered to be a function of exposure time above critical concentrations.[6]

Consequently, prolonged inhibition of topoisomerase I should be considered as

the important parameter in designing the dosing schedule for *in-vivo* cytotoxicity. In addition, Talwar and Redpath argued that the nature of the interaction of radiation and Taxol may be dependent on this phenomenon.[7] An examination of the data reported by these authors revealed that maximum cell killing occurred when the percentage of cells in G (1) phase was at a minimum at the time of addition of Taxol. Studies of Taxol-induced toxicity using cells synchronized in G (1) phase with mimosine and then released and allowed to progress through the cell cycle confirmed this observation.[7]

Data from Guichard and co-workers confirmed that prolonged exposure schedules presented less toxicity and greater anti-tumor effect of topotecan than high doses during short exposures.[6] The time during which plasma concentration was higher than 0.2 μM (target concentration) seemed to be critical for the topotecan anti-tumor activity, so maintaining this concentration for more than 10 h [(d x 5) x 4 schedule] exhibited the highest efficacy (100% of cured mice). In the schedules that did not maintain such a concentration during the same time period [dx1 and (d x 5) x 16 schedules], a lower efficacy was observed. By contrast, the high peak plasma level achieved after high doses of topotecan may have been responsible for the occurrence of lethal toxicity. Furthermore, prolonged intra-peritoneal and per oral administration of topotecan resulted in responses in xenografts that did not respond to a short term intra-peritoneal intermittent high-dose schedule, suggesting that prolonged administration could exert a greater cytotoxic effect on tumor cells.[6] These data confirmed those observed by Houghton et al. with irinotecan.[8] Reducing daily dose and increasing the period of administration appear to offer a therapeutic advantage in terms of both efficacy and toxicity.

In some circumstances, continuous infusion does not seem to be the optimal schedule, because this type of administration could down-regulated the target expression, which might constitute a mechanism of resistance to the drug. Then, repeated administration over a longer critical period should be favored.

Discussion

In a recent work, we conducted a pharmacokinetic characterization of six different intravenous vitamin C infusion dosage scheme given at high doses, following dose-escalation protocols (15 to 65 g, five cycles), in a 75-years old male prostate cancer patient (results submitted for publication). The results for this pilot pharmacokinetic study of vitamin C at high dose infusions, in a cancer patient, suggest a dual-phase kinetic behavior of ascorbate such as earlier reported in vitro.[9] This disposition pattern depends on the actual infusion-generated plasma ascorbate concentrations with respect to the saturation cut-off level (ca. 70μM = 0.123 mg/dL).

As Hickey and co-workers pointed out, the short half-life of vitamin C during the rapid excretion phase is sometimes ignored, particularly by the NIH's dose and frequency of intake recommendations.[10] Plasma levels above 70 μM have a half-life of approximately 30 minutes, so large doses taken several hours apart should be considered independent, as should be their bioavailability.[10] This cumulative pattern means that splitting a single large dose into several smaller ones, taken a few hours apart, increase the effective bioavailability of the large dose. This schedule-dependence phenomenon also needs to be taken into consideration for any further interpretation of ascorbate pharmacokinetic and pharmacodynamic results.

In another report from a colleague in Vermont, the following results were observed for 60 years old, 105 lb. female

breast cancer patient who is taking 10 g oral vitamin C in divided doses each day. The plasma ascorbate levels after infusion of 75 g over 75 minutes were 521 mg/dl. Strikingly, the same patient one month later was infused with 50 g in 30 minutes, and then continued with another 25 g over next 90 minutes, the resulted plasma ascorbate concentration at steady-state was 423 mg/dL. According to Dr. Warnock, the results suggest that once blood levels of ascorbate are established it is possible to maintain them over a period of time with a much lower amount. The infusion rate over first 30 minutes was about 1.6 g per minute and over the next 90 minutes was about 0.3 g per minute. Dr. Warnock is currently planning to extend the lower infusion rate out to 3 hours if the patient would consent and take another ascorbate level. Previously, this patient had been receiving 75 g of vitamin C three times a week for about 2 months but she did not seem to be making significant progress with her cancer (personal communication, Warnock; 2006).

Notably, in a recent survey using another dosing schedule, Dr. Warnock infused first 50 g over 30 minutes (i.e., initial dosage in the same female breast cancer patient) but this time he continued dosing 50 additional g of vitamin C intravenously within the next three hours. Reportedly, the ascorbate level at the end of the 3.5 hours and half was 355 mg/dL. Accordingly, Dr. Warnock concluded that using a higher infusion rate (i.e., 25 g per hour; 75 g total dose over 3 hours) he will be able to stay over 400 mg/dL indefinitely, and finally speculated about keeping a constant infusion going over 24, 48 or even 72 hours. In fact, the same schedule has been postulated by Drs. Miranda-Massari and González for intravenous vitamin C administration based on his own experience.

All these observations together are suggesting a schedule-dependence phenomenon in vitamin C pharmacokinetic–pharmacodynamic relationship. Perhaps, as it was earlier observed with antineoplastic drugs like topotecan and cytarabine, prolonged drug administration (over a critical infusion time, T) will results in a greater cytotoxic effect on tumor cells. Such response pattern could not be observed after a short-term intermittent high-dose schedule. That is, fractionating overall dose size and increasing the period of administration (exposure time, T) appear to offer a therapeutic advantage in terms of both efficacy and toxicity. It is assumed that the time during which the drug concentrations are maintained close to the "target concentration" seems to be critical for anti-tumor activity and highest efficacy. Sometimes, variables such as total dose size and the area under the disposition curve (AUC) are schedule insensitive and they are generally insufficient to adequately represent treatment strength.

Interestingly, Dr. Riordan and coworkers earlier reported that some cancer patients had complete remissions after high intravenous infusion dose of vitamin C, even though the concentrations of vitamin C that kill most tumor cells in vitro (200 - 400 mg/dL) were not achieved (immediately) after the infusion of 30 g of vitamin C.[11] Consequently, they argued that remissions in patients treated with this schedule are likely to have occurred as a result of vitamin C induced biological response modification effect rather than direct cytotoxic effects.[11] But, what if we look at the cumulative (net) vitamin C effect instead of the cumulative vitamin C concentrations? Again, we speculate about the schedule-dependence in pharmacokinetics of Vitamin C to account for such a discrepancy.

Levine et al. (1996) argued that the determinants of the recommended dietary allowance (RDA, based on the Food and

Nutrition Board of the Institute of Medicine criteria) for vitamin C include, among others, the relationship between vitamin C dose, steady-state plasma concentration, tissue store or cell compartments concentration/distribution, and urinary excretion. As the authors stated, these factors could account for the sigmoid shape of the dose/plateau plasma concentration curve they found in their vitamin C depletion-repletion pharmacokinetic study.[12] Accordingly, in the event that a larger vitamin C distribution into cellular compartments occurs, like in disease-states or stress conditions, it is logical to expect a shift-to-the-right in the curve and, consequently, in the dosage recommendation (saturation cut-off). That is, the steep portion of the curve will occur at a daily dose greater than 100 mg, the first dose beyond the sigmoid portion of the curve might be larger than 200 mg daily, and complete plasma saturation could occur at more than 1,000 mg daily. This is due to the kinetic connection between plasma and tissue ascorbate concentrations (plasma to tissue compartments).

Tissue stores are thought to be near saturation at 60 mg, and increased excretion would occur at higher doses. This information is supported by studies with healthy young humans, therefore the conclusions are based on facts that need to be revised for patients with damaged tissues (e.g., cancer cells), which are demanding higher levels of ascorbate (at millimolar range) than healthy cells are.

Vitamin C is accumulated in cells in part by a sodium-dependent transporter with saturable kinetics. The transporter achieves Vmax at approximately 70 μM, the same plasma ascorbate concentration achieved by ingestion (orally) of 200 mg daily in healthy volunteers. The RDA yielded a plasma concentration of approximately 24 μM, similar to transporter KM of 5-30 μM.[12] Small changes in concentration at transporter KM yield large changes in amount transported, behavior predicted by Michaelis-Menten kinetics. Kinetic and biochemical data imply that ideal vitamin C ingestion should yield a plasma ascorbate concentration above the KM of the transporter. Probably, 200 mg daily produced this plasma concentration in healthy young men, but for cancer patients higher doses might be required. Notably, the saturable kinetic for ascorbate distribution into cells call for slower intravenous infusion of high vitamin C dose and this scheme coincides with what we previously established regarding the schedule-dependence phenomena (i.e., prolong drug administration over a critical infusion time).

Conclusion

In consideration of the presented evidence, we recommend that any further clinical protocol for assessing the kinetic response of vitamin C in cancer patients should be conducted based upon the schedule-dependence approach, as necessary corroboration with experimental data is mandatory. In addition, the use of turnover concept and indirect response modeling for vitamin C pharmacometric analysis also needs further discussion.

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