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## EDITORIAL

### The Calculation of Received Dose Intensity

**I**N ANIMAL model systems of cancer chemotherapy, it is possible to characterize each drug with respect to the doses that produce no antitumor response, doses that produce some response, and doses that produce varying degrees of fatal toxicity.

In humans, treatment is usually given in combinations of drugs, in multiple doses, and by varying schedules spread out over time, while toxicity is avoided by varying schemes of dose attenuation and treatment delay. In this situation, the concept of dose intensity allows rediscovery of drug dose-response relationships. By taking into account the time element, and describing the drug delivery as milligrams per square meter per week, treatment delay and dosage reduction can each be accorded importance. In the case of drug combinations, one of the combinations can be arbitrarily chosen as the standard, and the approach still applies. Retrospective studies show that outcome is strongly correlated with dose intensity, particularly the amount of drug actually received (received dose intensity) for some drugs or drug combinations in some diseases.<sup>1</sup> A distinction is impossible to make between total dose and dose intensity from such retrospective analyses because, in the trials analyzed, the duration of treatment and therefore the total dose have not usually been controlled.

Thus, prospective randomized trials are required to determine where and to what extent dose intensity determines outcome, and to what degree the total dose is a determinant of outcome

independent of dose intensity. To partially overcome this difficulty in retrospective analyses and to properly analyze received dose intensity in prospective studies, the most practical method of fixing the total amount of drug intended to be given is to fix the number of cycles used for the analyses. In the case of retrospective studies, one can specify the number of cycles to be analyzed from a judgment as to what would constitute a fair test of the treatment with respect to the outcome measurement selected (remission induction, for example). In the case of a prospective study in which the total amount of drug should have been controlled, the number of cycles to be analyzed is the number of cycles in each arm.

In such analyses, it is critical to have a method for calculating received dose intensity that introduces the least distortions and uses all the data. It is also critical to apply the concept uniformly to allow comparisons between different trials and between difference analyses.

When we first began studying dose intensity, we decided that when inspecting for a within-trial relationship between dose intensity and outcome, dose intensity should be regarded primarily as a feature of an individual patient's treatment course and that average dose intensity for a group of patients should be derived by averaging these individual treatment courses. Received dose intensity was thereby calculated on a per-patient basis and averaged across patients, rather than across cycles. Furthermore, it was concluded that in order to apply the concept

in the most logical fashion, any method would have to account for all treatment delays.

The analysis of patient treatment that is truncated for whatever reason should have included for the purpose of calculation only the number of cycles they received up to the specified limit. Only "assessable" patients (patients getting through the first one or two cycles) could be included in the analysis, but this might exclude early progressors and would limit the value of the final result. The analysis could also be repeated to include all cycles the patient received, but this would introduce another artifact: responders will go on past the specified number of cycles, but dose intensity will drop due to cumulative toxicity.

The details of the method we have used and that addresses all of these issues are as follows: the total number of milligrams per square meter is determined for each drug given throughout the "course of treatment" (defined as the specified number of cycles determined as indicated above) for each patient. The denominator is then determined by counting the total number of days between the date of first treatment (cycle 1, day 1) and one cycle time after the date of the last treatment. The total number of days of treatment for that patient is then divided by seven to give the number of weeks, and this is used as the divisor to determine the patient's received dose intensity for each drug. In multiagent regimens, the figures are converted to average relative received dose intensity using an arbitrarily chosen reference regimen.<sup>1</sup> Patients are listed in an array, in order of received dose intensity (or average relative received dose intensity) with their response and survival opposite, together with any other descriptors deemed relevant. The array is scrutinized to detect the relationship, if any, between received dose intensity and outcome for the entire group or subsets within the group. The average received dose intensity for each drug is the arithmetic average of the final received dose intensities for all the patients in the array, regardless of how many cycles of therapy (within the specified limit) they received as individuals.

In the present issue of the *Journal of Clinical Oncology*, Miller et al<sup>2</sup> have used a different

approach. We have avoided their approach because of the problems it creates. For example, their method of using a fixed time period, or their method of handling of treatment delays, will falsely increase the calculated received dose intensity: the fewer the cycles of therapy, the worse the distortion. Patients taken off therapy were considered by Miller et al to have zero dose intensity during subsequent intervals. This falsely decreases the calculated received dose intensity. Furthermore, averaging across cycles instead of patient courses tends to obscure any within-study relationship between received dose intensity and outcome for individual patients or groups of patients.

In addition, Miller et al have introduced a separate term called "dose rate" as if it were a separate entity, but what they are describing is a component already integrated into the calculation of dose intensity. We suggest the term dose rate be reserved to describe the rate of administration of the drug at the time each dose is given. It could be expressed as milligrams per square meter per minute. This would make the term analogous to dose rate in radiotherapy (rads per minute). Used in this sense, dose rate may be a very significant variable, since it may determine peak drug levels which govern some types of toxicity.

One can reasonably ask, are these methodologic niceties important? Even though distortions of the estimation of received dose intensity will occur and within-trial correlations will be missed if the method of Miller et al<sup>2</sup> is used, in conventional chemotherapy ranges the difference in received dose intensity calculated by the two methods may not be large. Why bother with such differences? We are entering the era of mega-dose-then-stem-cell rescue. The differences will become magnified the fewer the cycles of treatment and the more intense the treatment. The differences are not trivial.

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