Evaluating Cancer Chemotherapy by Infusion

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For the vast majority of antineoplastic agents, the optimal schedule of administration has not been established. The reasons why the safety and effectiveness of cancer chemotherapy might be schedule-dependent are multiple and complex. Perhaps the simplest is that many anticancer drugs have their greatest effect when cancer cells are progressing through the cell cycle (particularly when in S phase) and are relatively ineffective when cells are quiescent in the G₀ phase. Since the common cancers in man have a low growth fraction and proliferate slowly, one of the important variables to be explored in clinical cancer chemotherapy is the duration of time that the exposure of malignant cells to the actions of antineoplastic drugs can be maintained. The relative importance of this variable and the manner in which exposure to the drug effect can be most effectively prolonged vary greatly depending on the clinical and biochemical pharmacologic characteristics of the agent in question.

Recognition of these facts has led to classification of antineoplastic agents on the basis of whether their cytotoxicity is cell cycle dependent or independent (1) or, alternatively, whether the drug effects are predominately dependent on 1) the maximum concentration of drug achieved; 2) the total exposure to drug, as measured by the plasma concentration times time product (C X T); or 3) prolonged exposure to cytotoxic drug concentrations for longer periods of time (2). The basis for this classification is that, experimentally, some antineoplastic agents appear to kill cells in all phases of the cell cycle; for these agents the magnitude of the effect generally appears to be related either to the peak concentration of drug achieved or to the extent of the overall drug exposure as measured by the C X T product. Other agents are highly phase-specific and have no effect on cells that are not in sensitive phases of the cell cycle. The magnitude of their effect is therefore likely to be dependent on the duration of exposure to a concentration of drug which exceeds a minimal cytotoxic threshold, and not simply on total exposure.

Although this distinction represents a gross oversimplification of the in vivo clinical situation, it helps to elucidate the characteristics of drugs that may warrant evaluation in continuous-infusion (C.I.) schedules of administration (3). The prolonged exposures provided by continuous infusion would likely be advantageous for antineoplastic drugs with a short plasma half-life, particularly if the intracellular mechanism of drug action is rapidly reversible in the absence of extracellular drug. In addition, prolonged exposure appears to be advantageous for drugs with mechanisms of action that are dependent on cells actively synthesizing DNA (S-phase specific drugs), for the treatment of malignancies with a low growth fraction, or for situations in which tissue penetration and cellular uptake occur slowly or in a time-dependent fashion. Antimetabolites, such as fluorouracil (5-FU) and cytarabine (cytosine arabinoside), represent the prototype drugs where the advantages of C.I. scheduling have been recognized. However, a large and expanding body of information indicates that broader evaluation of this approach may be warranted. Continuous-infusion schedules may also be preferred or required when the dose-limiting toxicity (i.e., nausea and vomiting, central nervous system effects, hypersensitivity, or acute cardiac effects) of an agent limits the use of bolus dosing. The classic studies of Legha et al (4) at the M.D. Anderson Cancer Center of anthracycline cardiotoxicity indicates that this advantage may extend to some chronic toxic effects as well.

The study by Goldberg et al (5) from the North Central Cancer Treatment Group (NCCTG) reported in this issue of the Journal describes the results of a randomized phase III study in non-small-cell lung cancer comparing etoposide (VP-16) and cisplatin continuous-infusion therapy with the more conventionally used rapid infusion or bolus therapy; in both regimens etoposide and cisplatin were administered over three consecutive days. The results of this carefully done study convincingly indicate that no advantage derives from the use of the C.I. schedule. On the surface these results seem surprising, since etoposide cytotoxicity has been shown to be highly schedule-dependent in a number of experimental and clinical circumstances. Human lymphoma lines in culture demonstrated a decrease in survival by an order of magnitude merely with a doubling of the exposure time to etoposide (6). In another system, a 50% level of cytotoxicity was achieved in a 24-hour exposure with concentrations of etoposide 1/100th of those producing the same effect in a 1-hour exposure (7). A similar advantage for repeated dosing schedules, which mimic C.I., has been seen in vivo murine tumor models (8,9). And most convincingly, several randomized clinical trials of etoposide in small-cell lung cancer have demonstrated a significant advantage for multiple daily administration schedules in comparison to either weekly dosing (10) or 24-hour infusion (11). Clark et al correlated the improved response rates seen in their trial with the duration of exposure to etoposide in concentrations exceeding 1 μg/mL (11); unfortunately, longer C.I. schedules for etoposide were not evaluated. Since the terminal half-life of etoposide in plasma is relatively long (7 to 11 hours), one might logically question whether C.I. is necessary to maintain a prolonged exposure to cytotoxic concentrations of drug (12).

The current study does not address that question. The pharmacologic and pharmacodynamic difference between a

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1 Growth fraction = percentage of cells in the tumor that are actively dividing or are in interphase.

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once-per-day dose of etoposide for 3 days and a 72-hour infusion of the same dose may not be sufficiently different to expect to see a difference clinically. The data from the ongoing NCCTG study in small-cell lung cancer, a disease more sensitive to etoposide, will be of great interest in this regard. An alternative design for the current study might have utilized either a longer C.I. period or a more protracted multiple daily dose schedule to examine the question of exposure duration more definitively. A daily oral schedule of etoposide over 21 days has produced responses in patients with disease that is resistant to conventionally administered etoposide (13).

The rationale supporting the use of C.I. cisplatin is less convincing. Several in vitro models appear to show an advantage resulting from prolonged exposure, while others show no difference (14,15). In the in vivo murine L1210 model, no advantage results from the C.I. schedule (16). Some clinical pharmacologic studies in man indicate that the CXT product of the free platinum species in plasma (the active form of the drug) may be increased when cisplatin is given by C.I. (17); however, this effect has not been found uniformly. The principal advantage of continuous infusion therapy with cisplatin may be an improved therapeutic index, as a result of the decreased gastrointestinal toxicity usually seen when cisplatin is given in this manner. It is possible that the greater myelosuppression seen in the C.I. arm of the Goldberg study is partially attributable to cisplatin, which appears to be more myelosuppressive when given in this schedule. There is no question that cisplatin has shown antitumor activity in a number of diseases when given by C.I. for durations of 24 to 120 hours. However, there are no clinical studies that demonstrate convincingly or even suggest an advantage for this schedule. Therefore, the inclusion of C.I. cisplatin in the study of Goldberg et al (5) adds an additional variable which one might consider an unnecessary and confounding one.

The authors of the Goldberg study recognized that although there were potential clinical advantages based on experimental results previously cited (see refs 6–17) for continuous infusion of etoposide and cisplatin, this approach could be established only by a properly designed randomized controlled clinical trial. However, not all standard chemotherapy regimens should necessarily be reevaluated in phase III studies with their “continuous-infusion equivalents.” In fact, studies of single agents or studies where a single drug is given by CI. may be preferred since the results may be more easily interpreted.

Several criteria should be satisfied before one embarks on such clinical studies. For the Goldberg study of etoposide and cisplatin therapy in non–small-cell lung cancer, these conditions were largely fulfilled: 1) Since etoposide and cisplatin combination therapy is considered one of the “standard” (or at least most commonly used) regimens used to treat non–small-cell lung cancer, efforts to optimize its effectiveness are important. 2) The collective experimental data provide support for the hypothesis that the effects of these drugs are synergistic and may be maximized by prolonging exposure.

3) Finally, the authors had preliminary pilot phase II data from the experimental arm of the study which suggested an improvement in response rate associated with the C.I. schedule (18). Future studies of C.I. scheduling should be supported by a similarly strong pharmacologic and experimental rationale; otherwise, phase III trials may consume clinical trial resources that could be directed more productively elsewhere.

References

(17) BELIVEAU JF, POSNER MR, FERRARIE ET AL: Cisplatin administered as a continuous 5-day infusion: Plasma platinum levels and urine platinum excretion. Cancer Treat Rep 70:1215–1217, 1986
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