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Editorial

Dose-response curves after in vivo experimental chemotherapy: Influence of rouze of administration on biological outcomes

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Curves that relate the biological response of an organism, tissue, or cell population to the amount of cytotoxic drug applied (dose-response curves) are a basic tool of the experimental chemotherapist. Almost universally, the independent variable of such dose-response curves is the administered dose (usually expressed as milligrams of drug per kilogram of body weight or per square metre of body surface area). While convenient, this practice ignores the possible interactions of route of drug administration, subsequent pharmacokinetics, and tissue organisation that result in the (usually unknown) amount of cytotoxic moiety that actually determines the final biological outcome.

Four examples are taken from the literature, in which such considerations influenced the quantitative and qualitative interpretation of biological response measured as a function of administered dose. All are for single doses of drug and all for treatment of mice. Van Putten et al. [4] injected BCNU either IP or SC and measured the survival of primitive clonogenic cells (CFUs) of the bone marrow. The CFUs were in their normal, largely resting state or had been induced to proliferate prior to BCNU treatment. The reciprocal of the slope of the cell survival curve (D_0) for normal CFUs was 3 times higher for IP than for SC BCNU, but only 1.4 times higher for proliferating CFUs (Fig. 1 A). Thus the ratios of D_0 (normal: proliferating) predicted by the two routes of administration were different: 1.5 : 1 for IP but 3.3 : 1 for SC. A second study [2] compared the response of clonogenic cells in different tissues to mechlorethamine hydrochloride, injected either IP or IV. For IV injection, it might be concluded that CFUs of the bone marrow were very much more 'sensitive' than microcolony-forming cells of the small intestine, because of the absence of an initial shoulder on the curve for CFUs (Fig. 1 B). In contrast, after IP injection the survival curves for these two cell types were very similar, the CFUs now being slightly more 'resistant'.

The biological outcome of chemotherapy may be conditioned by the anatomy of a tissue. For mice treated by IV adriamycin the survival curves for tubules in the centre of the murine testis and for peripheral tubules underlying the testicular capsule, were very similar (Fig. 1 C [3]). After IP injection, the shapes of survival curves varied systematically across the testis, with the shoulder on the curve becoming progressively smaller and the D_0 progressively larger from the centre to the periphery of the organ. These variations are most readily explained by differences in drug

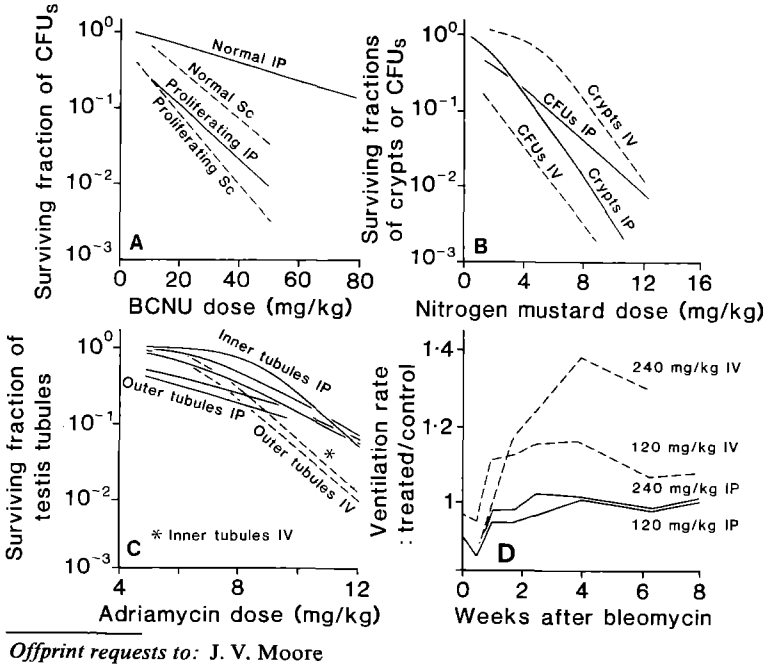

Fig. 1 A. Surviving fraction of femoral CFUs *(log ordinate)* versus administered dose of BCNU *(linear abscissa)* following injection by different routes (IP, SC), and for CFUs of different kinetic status (normal or proliferating). Redrawn from [4]. **B** Surviving fraction of femoral CFUs and of crypts of the jejunal mucosa versus administered dose of mechlorethamine hydrochloride injected either IP or IV. Redrawn from [2]. **C** Surviving fraction of cross sections of testis tubules versus administered dose of adriamycin injected either IP or IV. *Solid lines* are survival curves for tubules in mice treated IP; *upper curve* for tubules in the centre of the testis, sequentially *lower curves* for tubules progressively nearer the periphery of the testis. Redrawn from [3]. **D** Ratio of lung ventilation rate (treated: control) on a linear scale, versus time after bleomycin (linear), for different routes of injection (IP or IV) and for two different doses of drug. Redrawn from [1]

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availability in the different regions of the testis after the two different routes of administration [3]. Where assays of cellular response to chemotherapy are not available, assays of tissue function are commonly used. Here also, response may be strongly influenced by methodology. Collis et al. [1] measured the lung ventilation rate of mice treated with bleomycin. Results for the IV route predicted a high degree of 'damage' (high treated: control ratio for ventilation rate) and a strong dose-dependence of the effect, whereas IP injection of the same doses caused little injury and the effect was apparently not dependent on dose (Fig. 1 D).

Assays of the type described above were developed initially to measure the response of therapeutically important normal tissues to ionising radiation, although they are being used increasingly to measure the response to cytotoxic drugs. For irradiation of cells in situ the shapes of curves of cell survival versus dose of radiation are regarded as reflecting primarily the fundamental biology of the irradiated system, because the quantity of radiation that is administered (the exposure dose) and the amount of energy that is imparted to a mass of given tissue (the absorbed dose) bear a constant relationship. It is suggested here that similar relationships have yet to be established for cytotoxic drugs and that greater consideration should be given to methods of measuring dose within the tissues for which the clonogenic cells are being assayed.

References

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