A Methodologically Improved Definition of Chemosensitivity Indices

Predictive assays for measuring chemosensitivity of human tumors to various anticancer drugs are a challenging problem in clinical cancer research today (2, 4, 8, 10). At present, there are mainly 2 predictive techniques suited for clinical routine work and for tailoring an individual patient's chemotherapy, namely, the agar cloning assay (3, 6, 8) and the biochemical antimetabolic assay (1, 4, 9). For in vitro testing of antineoplastic agents, sensitivity indices are derived from dose-response curves and are used to measure chemosensitivity relevant to in vivo conditions. Most investigators (8) use the method of Moon (5) to define a sensitivity index (S) for each single drug. S is defined as follows. Assume that the doses (concentrations) $c_1 < \ldots < c_{\text{max}}$ are used. Let $Q(c)$ be the "effect" at $c_i$ expressed as percentage (e.g., death, inhibition) of the treated sample, and let $P(c) = 100 - Q(c)$. Then

$$S = \int_0^{c_{\text{max}}} P(c) \, dc$$

where the $c$-axis is the linear concentration scale and $P(c)$ is the function obtained by connecting the points (0, 100) and $(c, P(c))$ by straight lines (chart 1). In other words, $S$ is the area under the (specially defined and approximated) dose-response curve.

In our opinion, 2 objections can be raised against this definition of $S$. (a) It is counterintuitive, in that high effects correspond to low values of the index. (b) It depends on the concentration scale and, specifically, on the highest concentration ($c_{\text{max}}$) used. Thus, values of $S$ arising from different experiments are hardly comparable. We propose a modified index, which measures relative effect rather than absolute:

$$S' = \frac{(100 - c_{\text{max}}) - S)}{S}$$

Chart 1 illustrates the definition of $S'$. It is easily checked that $S'$ is related to $S$ by a strictly monotonic (order-reversing) function.

Because $S'$ depends on the shape of the dose-response curve, a reliable determination of $S'$ just as of $S$ (Ref. 5, p. 218), requires sufficiently large upper concentration limits. If $c_{\text{max}}$ used in the defining formula for $S'$ is chosen minimal such that the corresponding negative slope of the dose-response curve is below a fixed (generally used) constant (whether or not the curve has a plateau, such a point will always exist), then $S'$ does not have the shortcomings mentioned above. Hence, its application should contribute to the comparability of the results of chemosensitivity assays and their relation to in vitro studies.

U. Abel
Tumorzentrum Heidelberg/Mannheim Inst. 09, DKFZ Im Neuenheimer Feld
6900 Heidelberg, West Germany

M. Kaufmann
Universitäts-Frauenklinik Vossstr. 2
6900 Heidelberg, West Germany

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U. Abel and M. Kaufmann


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