Variation in Selective Toxicity: Causes and Consequences

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Summary

Variation in selective toxicity is a fundamental consequence of the neoplastic process and seriously limits the value of predictive tests. This variation is due to the biochemical heterogeneity of animal and human host-tumor systems, to the heterogeneity of drugs with respect to those factors which are required for maximum selective effect, and to the low therapeutic indices of many anticancer drugs. It is suggested that this problem can be overcome either by use of drugs with high therapeutic indices or by treatment based on the biochemical peculiarities of each individual host-tumor-drug system.

An ideal cancer chemotherapeutic agent must not only exhibit a high degree of selective toxicity, but must in addition be selectively toxic in a regular and predictable manner. The current slow progress in cancer chemotherapy is certainly due in part to a dearth of highly selective drugs, and the design, synthesis, and testing of new compounds with higher degrees of selective toxicity must continue. At the same time, however, it must not be forgotten that a large number of compounds with fairly high degrees of selective toxicity have already been identified in test systems although most have not proven useful in clinical practice. Selective toxicity per se is, therefore, not the only problem, and an equally important difficulty may be this variation in selective toxicity from one system to another. Increasing variation in selective toxicity is of course accompanied by decreasing predictability of drug effects. This paper will attempt to deal briefly with three questions: (a) How serious is the problem of variation in selective toxicity? (b) How do the current major approaches to cancer chemotherapy deal with this problem? and (c) Are other approaches possible?

Two types of variation in selective toxicity are especially evident. The first is among different human patients treated with the same drug. Variation in response to chemotherapy may occur among patients with different forms of malignant disease, between the primary and metastatic forms of the same tumor, and even among patients whose clinical situations are very similar. One must ask whether this variation is a secondary problem which can be overcome by new drugs and better use of current drugs or if, instead, it is a basic feature of the cancer problem which requires new approaches.

The type of variation in selective toxicity to which most attention has been paid, however, is that between animal tumor systems in general and human cancer patients in general. The diminished predictive usefulness of the animal screening systems which is consequent upon such variation is obvious and is a major concern to all. Again, one must ask whether this variation is a secondary problem which can be overcome by manipulation and improvement of the screening systems or if, instead, it is a basic problem which requires radically new solutions. Some would indeed say that the present type of screening program is totally inadequate and should be discarded immediately. Others assume that the problem of variation in selective toxicity will disappear if only the right animal tumor is used for screening. In neither case have the implicit assumptions behind these views been examined critically and in depth, and it is unfortunate that there are available so few experimental data which bear on this subject.

The inevitable emphasis on the variation in selective toxicity between animal tumor systems and human cancer patients, and among human patients with neoplastic disease, tends to obscure a number of other types of variation in selective toxicity, the consideration of which may help to clarify this problem.

A single drug which has good selective toxicity in a given experimental host-tumor system may, at the same dose, be quite ineffective against the same tumor or more toxic to the same host if either the route of administration or dose schedule is changed, or if the tumor is in a different form or location, or if it is in a different size at the beginning of therapy. It is also recognized that there is a normal statistical variation in drug effects within a population of animals bearing such a sensitive tumor. There may be in addition a change from year to year in the drug sensitivity of a given transplantable tumor, due to slight shifts within the population of tumor cells. The well-recognized phenomenon of true drug resistance is often a consequence of a variation in selective toxicity due to drug-induced shifts in the tumor cell population.

It is obvious that different tumors in the same animal strain may respond differently to drug treatment and that various animal strains and species may differ in sensitivity to drug toxicity. Age, sex, nutritional status, and the presence of another disease are sometimes important variables in selective toxicity, as is the history of previous treatment, especially by radio- or chemotherapy. Finally, the growth rate and duration of the various stages of the cell cycle may also be significant variables in the selectively toxic action of drugs.

A consideration of these well-known observations tends to lead to the conclusion that variation in selective toxicity is the rule in cancer chemotherapy, not the exception. Except for...
the problem of drug resistance, the significance of these observations for the treatment of human cancer have frequently been ignored or underrated. Variation in selective toxicity among animal host-tumor systems has often been considered, at least implicitly, to be both quantitatively and qualitatively different from the variation observed between animal screening systems and human patients, and among human patients. The pharmacologic and biochemical bases of these different types of variation in selective toxicity must, however, be fundamentally similar.

Variation in drug toxicity towards tumor cells is due to the tremendous biochemical heterogeneity of tumors; this individuality, unfortunately, tends in practice to be underestimated due to the unavoidable use of histologic classifications and through a natural attempt to prevent chaos. The individuality of tumors arises first from the unique heredity of each cell of origin and in its special differentiation and unique microenvironment. At every stage of tumor growth the random biologic and biochemical changes of tumor progression may occur. Changes in growth rate, fraction of actively dividing cells, characteristics of the cell cycle, invasive character, and tendency to metastasize may occur at the biologic level. At the biochemical level both qualitative and quantitative changes in enzyme activities may occur; these may be called changes in biochemical control mechanisms, if this term is taken in a broad sense. Because of these very fundamental aspects of the neoplastic process, therefore, tumors may differ not only from individual to individual, but also in time. This variation is frequently not detectable at the histologic level, and it is unfortunate that microscopic anatomy is the only scheme presently available for the classification of tumors. Slight variations in enzyme patterns which exist within tumors of apparently identical morphology may have very important consequences for the metabolism of anticancer drugs.

Variation in drug toxicity towards host tissues is due first to species differences and secondly to individual variations among members of one species, including those of age, sex, and nutritional status as well as genetic variation. The host, and host variation, must be very important in cancer chemotherapy. Most of a dose of drug is distributed among the normal body tissues, and the major mechanisms for storage, inactivation, and excretion of drugs are in the host rather than in the tumor.

The pharmacologic bases for variation in selective toxicity must likewise be fundamentally similar in all cases. To be toxic to tumor cells, the drug must be present in its biochemically active form at the site of action at a suitable concentration and for a suitable period, and it must interact with a biologically important target. In order to be nontoxic to host tissues, one or more of these requirements for drug action must not be met. Quantitative or qualitative variation in any of the many factors which influence toxicity to the tumor cells or lack of toxicity to the host tissues may lead to a variation in selective toxicity. The concentration of active form of drug in host or tumor cells is a function of the amount that reaches them from the site of drug administration, of their activating and inactivating activities, and of their intrinsic sensitivity to drug action. Some recently obtained data which illustrate some of the factors involved in variation in toxicity of one-half of the host-tumor system are shown in Table 1. As shown

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>Route of drug administration</th>
<th>ID_{50} (mg/kg)</th>
<th>Maximum drug nucleotide concentration at ID_{50} (mumoles/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneum</td>
<td>Intraperitoneal</td>
<td>17</td>
<td>3.04</td>
</tr>
<tr>
<td>Ascites</td>
<td>Subcutaneous</td>
<td>67</td>
<td>3.36</td>
</tr>
<tr>
<td>Axilla</td>
<td>Intrapertoneal</td>
<td>50</td>
<td>0.24</td>
</tr>
<tr>
<td>Solid</td>
<td>Subcutaneous</td>
<td>28</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Variation in toxicity of 6-mercaptopurine to the Ehrlich carcinoma.

many times previously by others, the dose of 6-mercaptopurine which results in 50% inhibition of growth (ID_{50}) varies greatly with the size of the tumor and growth and with the route of drug administration. This variation is due in part to the amount of drug which actually reaches the tumor and is converted to nucleotides. As would have been expected, for each site of tumor growth, the same maximum drug nucleotide concentration in the tumor was reached at the ID_{50}, regardless of the actual value of the ID_{50}. It was somewhat surprising to find, however, that the maximum drug nucleotide concentration at the ID_{50} was about 20 times higher in the ascites tumor than in the solid form of the same tumor. Although other explanations cannot yet be excluded, it would appear that the solid tumor is intrinsically more sensitive to 6-mercaptopurine than the ascites tumor. It will be of great interest now to measure drug nucleotide concentrations in host tissues under similar conditions.

Variation in selective toxicity is of course due not only to great individuality in the biology and biochemistry of host-tumor systems, but also to the relatively low therapeutic indices of most anticancer drugs. These two factors interact strongly because individual variations in tumor and host become more and more important as the differences between tumor and host upon which selective toxicity depend become smaller.

In answer to the question of how serious is the problem of variation in selective toxicity, it must be concluded that this is a fundamental consequence of the neoplastic process, and one which must be faced squarely if cancer chemotherapy is to progress. At the present time, unfortunately, we have very little information as to the biochemical bases of selective toxicity and, consequently, almost no information as to the bases of variation in selective toxicity.

Several different approaches are currently being made in attempts to increase the effectiveness of clinical cancer chemotherapy. How do they meet this basic problem of variation in selective toxicity? Both the continued use of the present type of screening system to find new and more active drugs and the optimization of dose schedules and routes of drug administration attempt simply to reduce the significance of variation by increasing the effective therapeutic indices of drugs. Therefore, they do not directly confront the variation.
problem but attempt to bypass it. There does not appear to be any firm experimental evidence that either supports or contradicts the view that it will be possible to increase effective therapeutic indices to a degree that renders variation in selective toxicity unimportant. Only subjective judgments can be made on this point at the present time, and it does not appear justifiable to support one side of this question much more strongly than the other.

Another approach is to attempt to establish new and better animal screening systems predictive for human cancer. This approach recognizes the problem of variation in selective toxicity in a general way, but it does not appear to appreciate its fundamental bases. Because of the individuality of both animal and human hosts and tumors, and the individuality of drugs with respect to the factors which affect their selective toxicity, it seems unlikely that an animal host-tumor-drug system of predictive value for human host-tumor-drug systems could be set up by the random choice of each of these three components as is now done.

The discussion to this point appears to cast serious doubt upon the predictive value of the screening systems which are presently employed. The suggestion of some critics that their use be discontinued does not yet appear to be justified, however. Although they do not seem to predict the drug responsiveness of human tumors in the manner which may have been desired, they do at least select drugs which are selectively toxic in one or more tumor-host situations. Rather than conclude that the whole screening effort is basically invalid, it may be suggested that the information provided by such systems has been misunderstood. It seems entirely possible that these systems do indeed select drugs that will be useful in clinical cancer chemotherapy, but instead of predicting direct and general usefulness of such compounds, they may predict only their potential efficacy. The real problem may then be one of how and when these drugs are to be used, and this information cannot possibly be provided by animal studies alone.

These considerations have led some to formulate an approach to cancer chemotherapy which directly meets the problem of variation in selective toxicity with drugs of no greater selectivity than now available. In this approach, potentially useful drugs would be matched rationally with the individual human patient-tumor situation in which each drug would be most effective and would have the greatest degree of selective toxicity. The basic premise of this approach is that a drug identified by the standard animal screening systems will have a good chance, if used properly, of being effective in at least one human tumor-host situation. This approach, therefore, demands less of the screening system but more of the biochemist and pharmacologist.

In order to identify the tumor against which a given drug could with most benefit be used, information is first required concerning the biologic and biochemical bases of selective toxicity of each drug in sensitive animal host-tumor systems. Then a wide range of variation and the bases of this variation must be explored, likewise, in available animal host-tumor systems. Finally, this approach would require biochemical information about the human tumor and host with respect to those factors found important for selective toxicity in the animal studies. The drug used for any particular patient would then be chosen mainly on the basis of the biochemical peculiarities of the tumor in question and the biochemical requirements of the drug for maximum effect, and with consideration given to its effects on and fate in the individual host.

Variation in selective toxicity seems to be a fundamental problem in cancer chemotherapy, and cancer research should confront it directly. The approach suggested would not discard the animal screening systems, but it would attempt to use the information they provide with more consideration for the basic difficulties of cancer chemotherapy and for the basic principles of drug action. Drug-sensitive animal tumors would not be required to predict the drug sensitivity of all human tumors, or of single histologic types of human cancer, but only of the human tumors which are biochemically similar to themselves with respect to those factors which are important for selectively toxic drug action.

It is readily admitted that the importance of variation in selective toxicity may diminish if new drugs of high selectivity are discovered. Is it really justified to expect this, however, or at least to expect it in the near future? Any attempt to confront the variation problem directly must of course admit our great ignorance of its biochemical bases at the present time. The problem is important, though, and it should not be as neglected as it now is.