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Perspectives and Commentaries

Evaluating and Designing Cancer Chemotherapy Treatment Using Mathematical Models*

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INTRODUCTION

CHEMOTHERAPY has revolutionized the treatment of some tumours. Unfortunately, in most of the common tumours success has been limited [1]. Many patients who initially respond to chemotherapy later relapse under continued treatment. A possible explanation is that resistance to the drug(s) being administered builds up as therapy progresses, until they become ineffective [2]. Other factors which may influence tumour response include the choice of drugs, the doses used and the timing of the drug delivery. A coherent picture of the relationships between these factors has never been drawn, and consequently many drug protocols are empirical in nature and the research clinician remains unsure of the best areas for investigation.

In this paper a mathematical model is introduced which is based on assumptions about these relationships and describes changes in tumour size under repeated drug therapy. It is designed to simulate new treatment strategies prior to their employment and so enable more rational treatment design. For individual patients the model may potentially throw light on awkward clinical decisions about when to delay, stop or change treatment.

The complexity of many previous mathematical models [3] has limited their clinical use. This model, however, has been developed for the purpose of clinical applications, the emphasis being on treatment strategy rather than detail. Interactive computer programs have been written so that the clinician can use the model quickly and easily. He can compare the results obtained with clinical experience, experiment on the computer with new treatment strategies and provide feedback to the mathematician on the aptness of the model's assumptions and its clinical utility. Graphs, such as those shown and explained in this paper, can be produced in a matter of seconds on a microcomputer.

Cytotoxic drug resistance is one of the main factors included in the model. It is conceived as having two components: some of the malignant cells are assumed to be resistant to the chosen drug(s) at presentation, while others develop resistance, as a result of, amongst other things, spontaneous mutation [4, 5] and host–defence reactions [4, 6] during therapy. The drugs, by definition, affect only the sensitive cells.

DESCRIPTION OF THE MODEL

In order to describe the changes in tumour volume throughout treatment, certain dominant factors (e.g. cell-kill and resistance) are selected and are related through the model [7]. The intention is to produce a simplified but broadly accurate picture of tumour response which lends itself to analysis.

Figure 1 represents the tumour as a mix of sensitive and resistant cells, and shows how, during the first two courses of a hypothetical treatment, they are affected by the therapy itself and by tumour growth. It is assumed that courses of treatment (of either a single drug or a combination) are administered at known intervals, and that (in line with experimental findings [8]) each course kills a constant fraction (k^*) of the sensitive cells.

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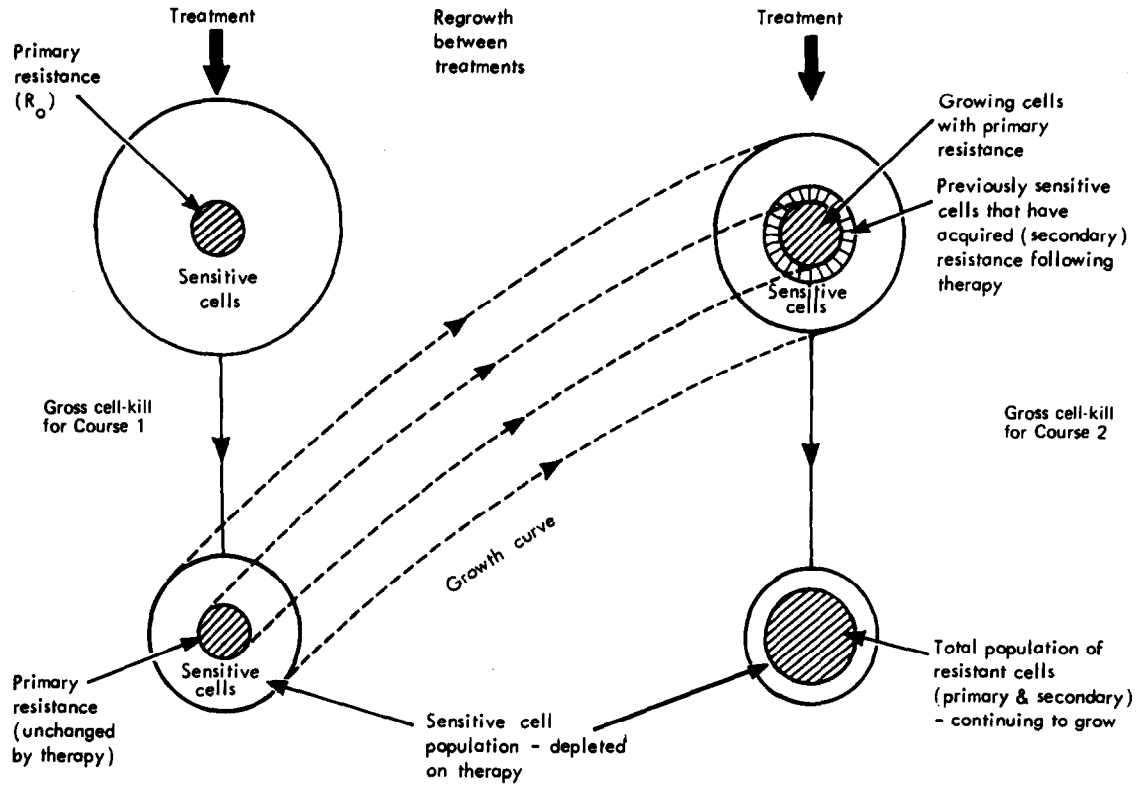

Fig. 1. *Diagrammatic representation of the model.*

The insensitive or resistant cells are assumed to remain unaffected by the treatment.

A proportion (R_0) of the initial tumour is assumed to be resistant from the outset (primary resistance) and a proportion (e) of the sensitive cells that survive each course are assumed to acquire resistance (secondary resistance). Cell-growth between cycles is assumed to obey some law, e.g. exponential or Gompertzian [9].

If both resistant and sensitive cells grow at the same rate, then as the sensitive cells are killed, resistant cells will form a larger proportion of the tumour mass (Fig. 1). The proportion of all cells killed with successive courses of chemotherapy will thus decline progressively (as shown in Fig. 2). This decline can be calculated for chosen values of the sensitive cell-kill and the primary and secondary resistance. For a particular growth law, corresponding changes in tumour size can also be calculated. A comprehensive account of the mathematical formulation is given in [7].

EXAMPLES

An example of how the model may be used for strategy testing is shown in Figs 2 and 3. Figure 2 plots the proportion of cells killed for each of several courses of therapy under two different hypothetical regimens. Values of primary and secondary resistance, initial tumour size and the interval between doses are assumed the same for each regimen, and only the value of the cell-kill, k^*, has been changed. This may correspond, for example, to the use of drugs of differing effectiveness or to the use of the same drug at different doses. Figure 3 shows the associated changes in the tumour (and, separately, the resistant tumour) cell populations.

For this example, the sensitive cell-kill values used, 95 and 75%, are in accord with the experimental findings of others [8], and with tumour regressions seen in many diseases during the early courses of treatment. The value for primary resistance is consistent with the spontaneous mutation rates assumed by Goldie and Coldman [5], while the secondary resistance proportion has been made arbitrarily large to demonstrate that its effect (shown by the curvature in the broken lines in Fig. 3) is greatest during the early courses. Exponential growth is assumed, with a tumour doubling time of 35 days, which is compatible with a fast-growing tumour such as small cell lung cancer.

It can be seen that the therapy with a high cell-kill depletes the sensitive cells rapidly, with dramatic loss of effect after only three courses (marked by arrows), while the therapy with a lower cell-kill is effective longer (the minimum tumour volume occurring after six courses), since it takes more courses to eradicate the sensitive cells (Fig. 2).

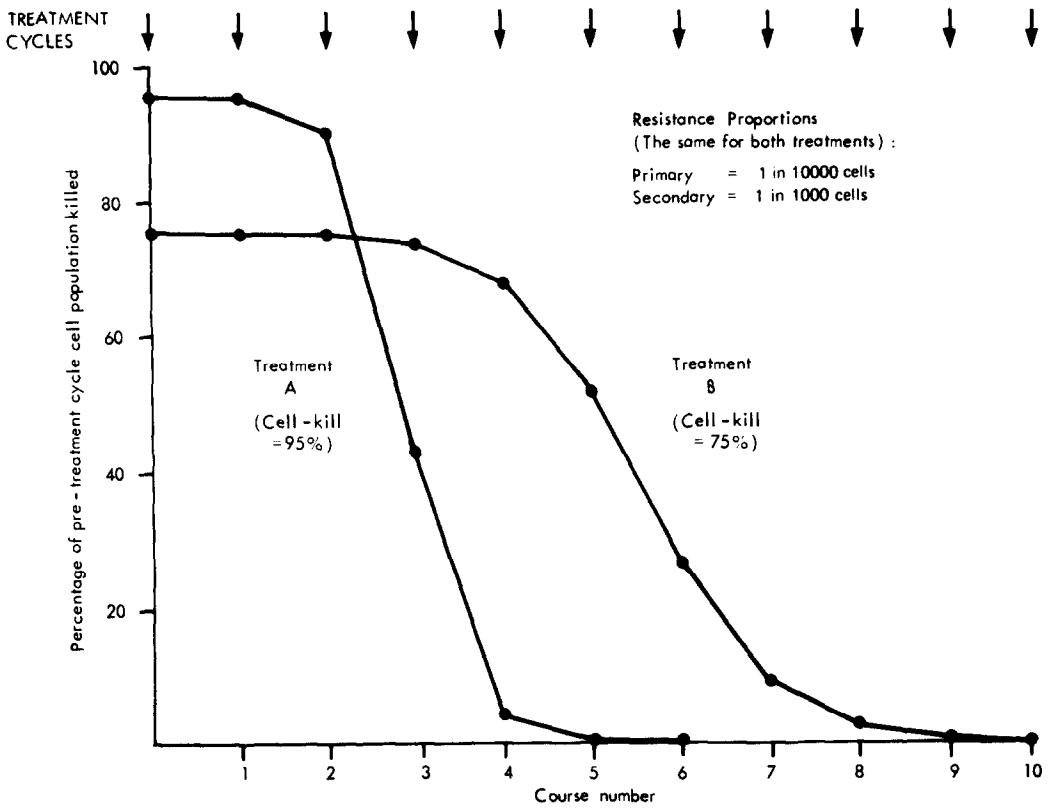

Fig. 2. Percentage of cells killed at each course for two different treatments.

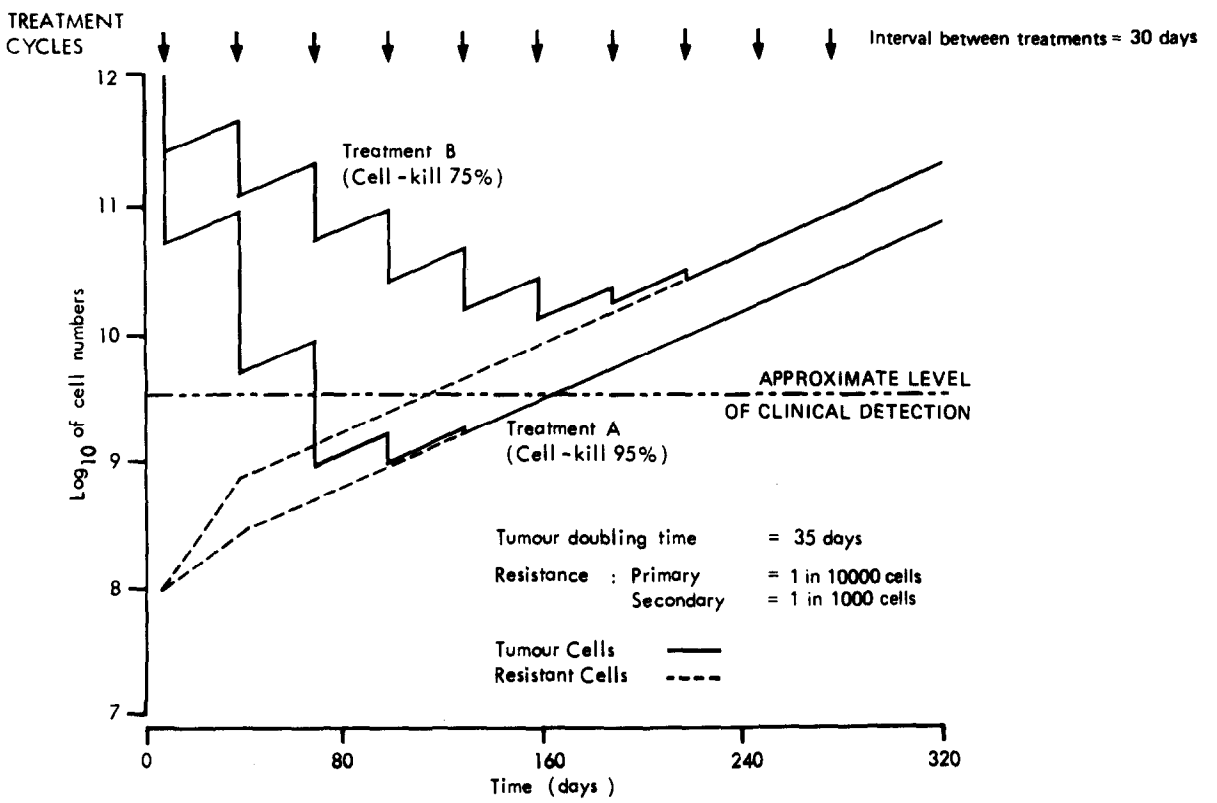

Fig. 3. Predicted tumour volumes for treatments with differing sensitive cell-kills.

POSSIBLE APPLICATIONS

The model is designed to embody the underlying principles of chemotherapeutic action on malignant cells. Its primary use is thus to provide a broad understanding of the reasons for the numbers and durations of responses seen in particular diseases, and to use this understanding to design and critically examine new treatment strategies. The model is not yet applicable to individual patients due to the difficulty of obtaining accurate measurements.

Comparison of treatment strategies

For a given tumour there will be a range of likely values for the cell-kill (k^*) and the primary and secondary resistance proportions (R_0 and e respectively) depending upon the choice of treatment [which includes drug(s), dose and schedule]. By changing the values of k^*, R_0, e and the intervals between courses the consequences of adopting different treatment strategies can be tested theoretically. For instance, the lowest tumour volume can be related to the interval between courses of therapy [7]. In Fig. 4 the effect of allowing an additional 20 days between cycles of treatment in a simulated trial is compared with giving the treatment on time, say after 30 days. It can be seen that in this case the main difference is in the lowest tumour volume attained.

Using the model for individual patients

If a reliable method of measuring tumour volume during therapy were available, the model could be used to estimate the levels of cell-kill, resistance and tumour doubling time for individual patients from as few as four successive measurements early in treatment. Predictions of the extent of response, the length of remission and the smallest obtainable tumour size under continued treatment could then be made.

The usefulness of computerized tomography (CT) for this purpose is currently being investigated in a prospective study, employing repeated scans before each course of therapy in selected patients.

Cross resistance

Alternating apparently non-cross-resistant regimens have recently been administered in an attempt to improve treatment results by overcoming resistance [10]. In some cancers such as Hodgkin's disease this has proved a promising approach [11], while in others such as small cell lung carcinoma it has given disappointing results [12]. It is difficult to evaluate the contribution of each drug in an alternating programme, but the basic model has been extended to address this problem [7].

Cells which are resistant to one drug, A, may also be or become resistant to another drug, B [10].

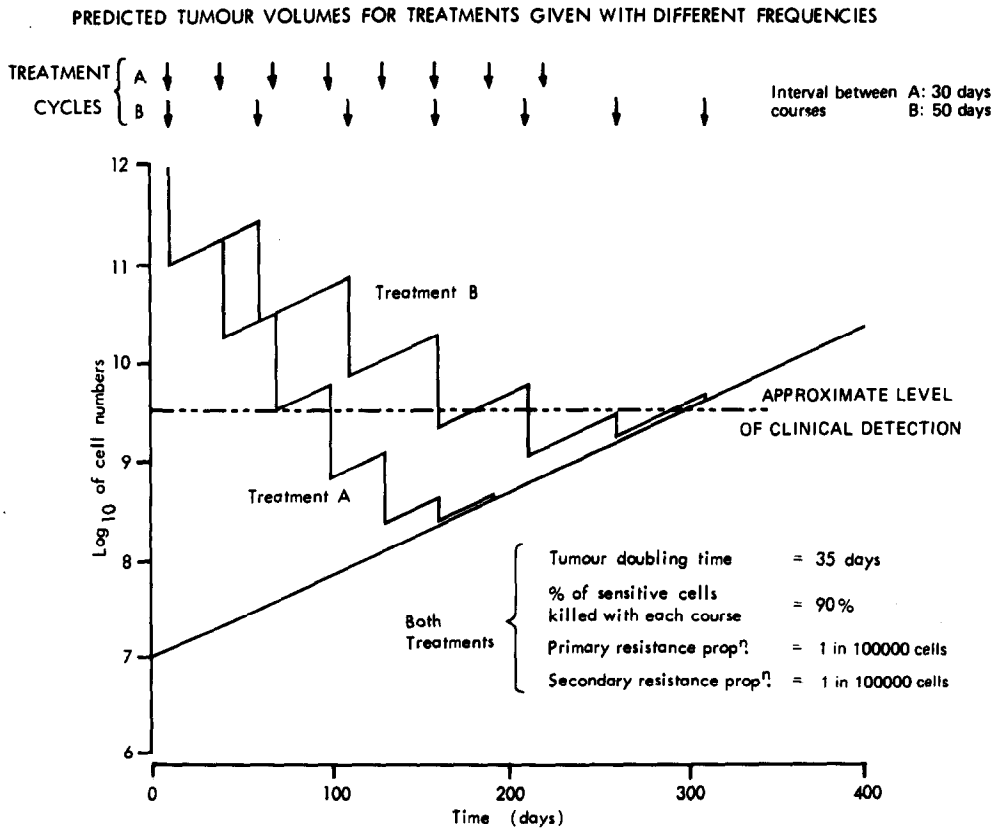

Fig. 4. Predicted tumour volumes for treatments given with different frequencies.

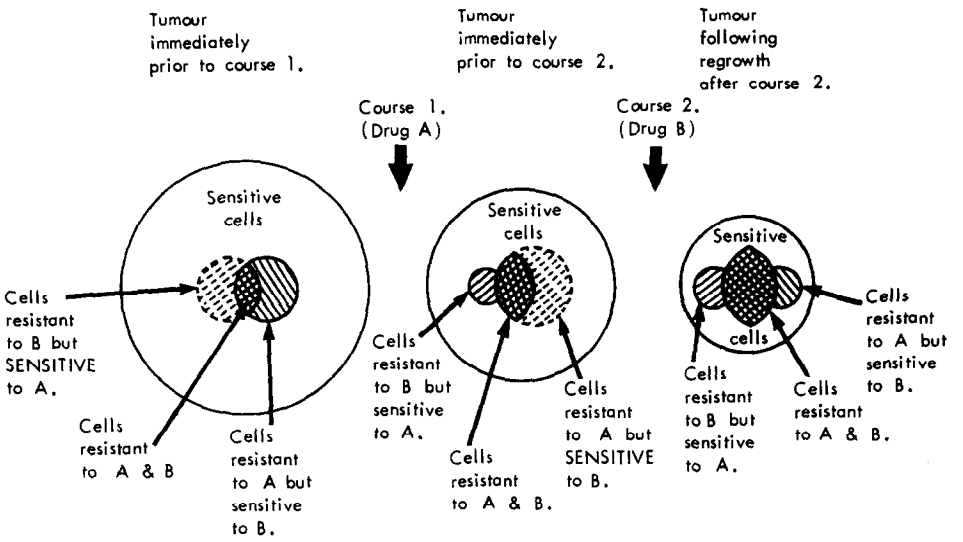

Fig. 5. Diagrammatic presentation of cross-resistance model.

The extent to which this occurs will be a measure of the cross-resistance between the two drugs. Under such circumstances there will be four populations of cells to consider: those resistant to drug A alone, those resistant to drug B alone, those resistant to both drugs and those sensitive to both drugs (see Fig. 5). By quantifying the changes in these groups of cells, in the same way as for the basic model, different treatment strategies involving two or more drugs can be simulated [7]. For example, repeated administration of the same drug can be compared with sequential delivery of two or more drugs between which there is some degree of cross-resistance, and so on.

In clinical practice it is very difficult to obtain more than an approximate idea of the degree of cross-resistance between two chemotherapeutic regimens. However, the model makes it possible to compare strategies by assuming different levels of cross-resistance. This alone helps to shed light on a problem that has previously been intractable, and provides at least some guidelines for the clinician. Making assumptions about cell-kill and resistance levels can reveal the order of magnitude of cross-resistance that must exist between drugs in order for them to achieve known durations of response. These calculations may suggest when the search for more highly non-cross resistant regimes is vital, or when other factors are more important.

DISCUSSION

This model of tumour response is at an early stage of its development. It rests on assumptions about cell-kinetics and the selection and outgrowth of drug-resistant cells during chemotherapy. It is not disease-specific and could eventually have widespread application.

In order to use the model to simulate treatment strategies, specific values must be used for resistance and cell-kill. In clinical practice, however, there is great uncertainty in these values for a given patient, and hence for groups of patients. The model must be extended to cope with such variability. This work and an investigation of the sensitivity of the model's predictions to departures from the assumptions is currently underway.

There is also scope to extend the model in other directions. Examples include investigations of the correlation between cell-kill and tumour doubling time (it is generally accepted that fast-growing tumours are more sensitive), and the inclusion of dose–response relationships.

Skipper *et al.* [8] attempted to define some general principles of cancer treatment by examining the underlying cytokinetic action of chemotherapeutic agents. Goldie and Coldman expanded on this early work by incorporating cell mutation rates and their relationship to resistance. The model presented in this paper is an attempt to bring these principles into closer touch with actual clinical practice by giving the clinician computerized models which he can experiment with in such a way as to explain and provide insight into some of his clinical results. Faced with a multitude of drugs and numerous possible treatment strategies, the clinician treating cancer with chemotherapy has a vast range of options open to him. By demonstrating some of the likely consequences of the hypotheses on which he builds his treatment regimens, mathematical models may assist in the design of more rational clinical investigations.

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