*Europ. J. Cancer*, Vol. 16, pp. 173–176
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0014-2964/80/0201-0173 $02.00/0

# Growth Delay and Tumour Relapse after Adjuvant Chemotherapy; the Validity of Models*

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VARIOUS models have been proposed to describe the loss of cells from tumours after exposure to cytostatic drugs *in vivo*.

The model used for L1210 leukemia by Skipper and his colleagues [1] at Southern Research Institute, has become known in the literature as the "log kill" model since it assumes that over a wide range of tumour loads;

(a) a constant fraction of the cells is killed after a similar exposure to drugs independent of the absolute number of cells initially present;

(b) the logarithm of the factor, by which the number of cells is reduced (log kill) by a drug, is proportional to the dose of the drug used.

This model was assumed valid also for solid tumours with a number of restrictions which were not quantitatively formulated: resistance to treatment could occur either on a cell kinetic basis, by development of a resistant subline of cells, or due to the tumour being located in a sanctuary where it is not reached by the drug.

More recently, Norton and Simon have attempted to quantify the predictions of cell kill when cell kinetic mechanisms are taken into account. In the first place they expanded the use of the Gompertzian tumour growth model as proposed by Laird [2, 3] and demonstrated that it is in better agreement with experimental data than the exponential growth model [4, 5] and they followed Lloyd's [3] assumption that the growth rate of a treated tumour is similar to that of an untreated tumour with a similar number of living tumour cells. Their main contention is, that cell kill is at each instant proportional to *GF*, the relative tumour growth rate [6]. On this basis they built a model which predicts an inversion point below which tumour cell kill becomes increasingly difficult and on this basis they assume an improved cure rate if higher drug doses are used at the end of treatment. They do, however, not quantify this therapeutic gain and a simple transformation of their model will show it nonexistent except for the very last drug dose, for which it is not greater than under the log kill hypothesis.

According to this model the relative increase in cell number per unit time is proportional to *GF* at each tumour volume. This implies that an increase in tumour cell number that is proportional to *GF* will take the same time, independent of tumour size. Since the model postulates that treatment causes cell loss proportional to *GF*, at each tumour size the time to compensate for this loss will be the same. This implies that a standard treatment will always cause the same growth delay, independent of the tumour size at which it is applied.† Now we can easily see the difference in effects of treatment between the log kill model and the Norton–Simon model; see Fig. 1. The first model assumes

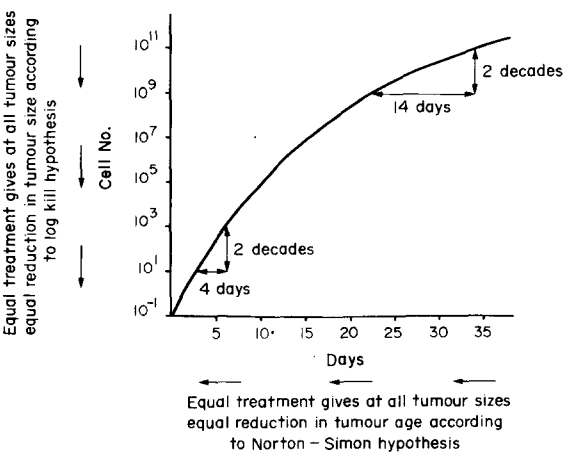


*Fig. 1. Schematic representation of the relation between cell kill and growth delay in a tumour growing following a Gompertz equation.*

Accepted 30 January 1979
*This work was carried out in the programme of the E.O.R.T.C. Screening and Pharmacology Group and financially supported by the Queen Wilhelmina Fund, Netherlands Organization for the Fight against Cancer.

†See mathematical formulation of this conclusion in appendix.

a constant distance displacement on the vertical axis of the graph: similar treatment decreases the log cell number to a similar degree. Since tumour regrowth in the intervals between treatment courses is faster at smaller tumour sizes, in this model treatment of smaller tumours is less efficaceous. The second model assumes a constant distance displacement along the horizontal axis, the time scale, and it reduces the "age" of the tumour by a fixed time. If the age is less than zero time, a probability of cure may be calculated from the relation between time and cell number. It is obvious that on this scale there is no inflection point dependent on tumour size at the time of the first treatment. It is evident that any treatment will be effective as long as the growth delay per dose is longer than the time interval between doses. The only advantage of differences in scheduling lies in the fact that after the last drug dose the time of host recovery is not relevant in determining the cure rate. Thus, the last dose is limited only so as to permit host survival even if it causes a bone marrow depression which would delay additional treatment for a very long time, but this is equally true for the log kill model.

From this transformation it may be concluded that the Norton–Simon model does not necessarily imply a preference for a different dose schedule as claimed. There is, however, a further implication of our conclusion: we can test the model for its validity. Data of Norton and Simon have shown that the decreased cell kill in large tumours is an obvious improvement over the log kill model; further confrontation with experimental data is now possible since we can test it with growth delay as an endpoint. The durations of growth delay of post-menopausal patients with breast cancer, when treated with an identical treatment schedule in the adjuvant situation and after relapse have been published from Milano [7, 8]. The obvious discrepancy and even more so, the data on growth delay duration for pre- and post-menopausal women which are similar for the large tumours but very dissimilar for the adjuvant situation suggest that the Norton–Simon model is not valid for all clinical situations. Analogous discrepancies in a mouse tumour model have been reported from our institute [9, 10]. In addition, there is another reason for assuming the model too simple: there is evidence that some cytostatic drugs may also kill resting cells [11] and that cytostatic drugs do vary considerably in their relative effectiveness in killing proliferating and resting cells [12]. If some drugs kill resting cells, there will be a relatively greater efficacy on larger tumours in terms of this endpoint and this would cause extra growth delay for the larger tumours. A model based on this assumption would indeed show less response (growth delay) if the tumour is smaller and thus might indeed profit from an increase in drug dose towards the end of treatment. However, the killing of resting cells is not a property uniformly shown by all cytostatic drugs [12]. For this reason a more refined model might differentiate according to the type of treatment. On the basis of such refinement different hypotheses may be formulated but it has until recently been questionable whether too much refinement in modeling has any sense. There might be a lack of suitable clinical data to test the validity of too refined hypotheses.

Recently, however, relapse rate curves after adjuvant chemotherapy have become available and they are more suitable for testing such models. For this reason a number of predicted and observed relapse rate curves have been studied [13] and it is hoped that such studies may give further information on the validity of some of the hypotheses included in our models. An example of the type of curve that is generated on the basis of model hypotheses is given in Fig. 2. If

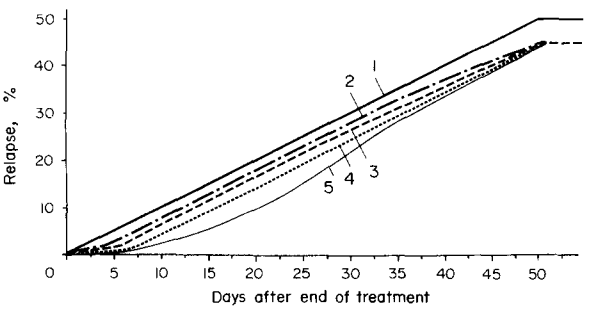


*Fig. 2. Theoretical relapse rate curve as affected by adjuvant chemotherapy. The control population is assumed to relapse at the rate of 1% each day (1). Adjuvant therapy delays the relapse rate in different ways and the four types are assumed to have received an intensity of treatment which causes, at 50 days, a similar level of final cures. If cell kill is limited to the fraction proliferating cells (~GF) by the use of ARA-C or MTX, growth delay is similar for all sizes of tumours, thus equal for early and late relapses (4). If large tumours have more growth delay due to the fact that resting cells are also killed, for instance by radiation or alkylating agents, the large tumours—which relapse early in the controls—show more delay (5). If, however, vascular insufficiency causes poor drug penetration in the larger tumours, the larger tumours causing the early relapses are less affected and curves 4 and 5 are transformed into 2 and 3, respectively. Note that the prediction concerns not the size of the effect, but the relative effect observed early compared to late after stopping treatment.*

drug action is only on dividing cells, our model predicts a growth delay and relapse delay similar to that of the Norton–Simon model, independent of the size of the tumour; so the relapse delay is similar for early and late relapses, although the former had a larger tumour load. Thus displacement in time is parallel for such drugs (Fig. 2, line 4). If also non-cycling cells are killed, the

larger tumours have more growth delay, so early relapses are more delayed and early results of adjuvant therapy promise more cures than will be realized upon late follow-up (Fig. 2, line 5).

Model studies, however, have suggested other alternatives: in Lewis lung tumour it is quite evident that for many cytostatic drug treatments the primary tumour hardly responds whereas there is marked response of metastases [14, 15]. Donelli *et al.* [16] have observed much lower drug levels in the large primary tumours of this type than in the small lung metastases. This would explain the poorer response of the large tumour. In the adjuvant situation the poorer response of the larger subclinical tumour would appear as an initially poor response to adjuvant therapy since the larger early relapsing tumour would show little difference between treated and control relapses as compared to the smaller later relapsing tumours (Fig. 2, lines 2 and 3). This pharmacokinetic type of resistance to treatment of large tumours (comparable to a "relative" sanctuary in Skipper's terminology) would invalidate the preference for large drug doses at the end of treatment.

This is even more so if we think of Skipper's other type of resistance, reportedly the most frequent cause of treatment failure.‡ It is the drug resistance due to the development of a small minority population of inherently resistant cells. Since the probability of development of resistance in cell populations as in microorganisms is likely to be proportional to their number, there is an at least equally good case to be made for giving high dose treatment early in the schedule.

‡See H. E. Skipper, *Southern Research Institute Booklet*, 3–11, (1978).

From these considerations we may conclude that it is at least premature to advocate modifying clinical treatment schedules to feature an increase of drug dosage with time.

It is obvious that mixing the cytostatic and pharmacokinetic variables will permit a wide spectrum of variable patterns of early and late response. Nevertheless, the clinical observation after adjuvant chemotherapy of an early growth delay, decreasing in size with time of observation can only be due to a larger growth delay of the larger tumour subgroup and this confirms the necessity of refining the Norton–Simon model. It is hoped that the analysis of relapse rate curves may contribute to our insight into the relative weight of different factors involved in treatment failure.

The theory makes, moreover, an important prediction, supported by animal model studies. The poorer response of the large Lewis lung tumour than of its small metastases points to the possibility of finding late effectiveness of adjuvant therapy in some diseases in which large recurrent tumours show a poor response. A logical candidate for this possibility could be found in human G.I.-tract tumours which respond poorly to chemotherapy and in which intensive adjuvant treatment failed to cause a response in the early years of follow-up. Recently, more encouraging (but not significant) results have been reported for the third year [17, 18]. Confirmation of these results would indicate the type of tumour for which, on the basis of its similarity to Lewis lung tumour in mechanism of response, adjuvant therapy could be successful even though chemotherapy of the primary or of the large relapsing tumour is still highly unsatisfactory.

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## APPENDIX

In the terminology used by Norton and Simon, their equation [7] may be written as:

$$\frac{dN}{dt} = (1 - K_5 L(t)) \cdot N \cdot GF(N),$$

where $N$ is tumour cell number, $L(t)$ = level of treatment given at time $t$ and $GF(N)$ is the specific growth rate at tumour cell number $N$. If treatment is given at level $L$ during a time interval $\Delta t$, the change in tumour volume $\Delta N$ will be:

$$\Delta N = \frac{dN}{dt}\Delta t = (1 - K_5 L(t)) N \cdot GF(N) \cdot \Delta t. \quad (1)$$

Normally $\Delta N$ will be negative representing a decrease in cell number. After therapy is stopped, the increase in cell number $\Delta N'$ during an arbitrary time $\Delta t'$ is:

$$\Delta N' = \frac{dN}{dt}\Delta t' = N \cdot GF(N) \cdot \Delta t'. \quad (2)$$

The original tumour volume before therapy is reached again when $\Delta N' = -\Delta N$. In that case the resulting growth delay time $D = \Delta t + \Delta t'$. By substituting $\Delta t'$ on the basis of equation (2), setting $\Delta N' = -\Delta N$ and substituting $\Delta N$ by use of equation (1) one obtains:

$$D = \Delta t + \frac{\Delta N'}{N \cdot GF(N)} = \Delta t - \frac{\Delta N}{N \cdot GF(N)}$$

$$= \Delta t - \frac{(1 - K_5 L(t)) \cdot N \cdot GF(N) \cdot \Delta t}{N \cdot GF(N)}$$

$$= K_5 L(t) \cdot \Delta t.$$

Thus $D$ is proportional to the intensity of treatment but independent of age or cell number in the tumour.

**Acknowledgement**—The author is indebted to Dr. J. van Best for the mathematical formulation of this conclusion.