ONCOLOGY

Tumor Growth Parameters of In-vivo Human Breast Carcinoma: A Proposed Mathematical Model for Tumor Growth Kinetics

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Many mathematical models have been proposed to study tumor growth parameters in *vivo*. Nevertheless most of the medical models have given variable results even when experimental conditions are exactly the same. There are multiple factors that are capable of affecting tumor growth that should be taken into account when proposing a mathematical model for tumor growth in *vivo*. We discuss here own proposed model for tumor growth kinetics utilizing a modified Gompertz function that better responds to the growth characteristic of in "vivo" tumors.

Key words: Tumor growth, Human breast carcinoma, Kinetics

In 1962 Mendelsohn (1) proposed the concept that tumors contain two populations of dividing and non-dividing cells. The fraction of proliferating cells was termed growth fraction; which in essence is the ratio of proliferating cells to the total number of tumor cells. The interaction between these two populations may determine the rate of growth of a tumor. In general when tumor cells are growing exponentially the growth fraction is said to be 100% but this may vary at different times and in different parts of individual tumors (2). It should be pointed out that tumors do not have a single growth rate but a growth rate that usually varies with the tumors age, location and environment. In summary we can assume that tumor growth is often irregular.

There are multiple biological factors that are capable of affecting tumor growth. These include but are not limited to: limitations imposed by blood supply, tumor hemodynamics, homeostatic regulation of tissue size, and the cumulative effects of cytotoxic products (3). Nevertheless there are basically two limiting biological requirements common to all stages of growth and those are the presence of physical and chemical essentials for all viability and the absence or low concentrations of cytotoxic and other inhibitory substances. Translating these facts in terms of tumor growth kinetics; two aspects seem to bear the most important influence on tumor growth: The growth fraction and cell loss.

Discussion

Tumor growth is studied by the use of kinetic curves. A kinetic curve is a graphical representation of changes in a certain value or characteristic of a process developing over time. Experimentally tumor kinetic curves are obtained by means of many data from a large number of tumors or animals with tumors. However kinetic curves can be plotted for individual samples as well.

Tumor growth in different animals carrying the same type of tumor will not produce exactly the same kinetic curve even if the experimental conditions are exactly the same (7). This lack of reproducibility is due to the variable proliferation of tumor cells resulting in large deviations from mean values. There is a great deal of heterogeneity present in tumor cell populations. This heterogeneity tends to increase with tumor growth (4). Nevertheless, since tumors are composed of cells; the earlier studies of tumor growth kinetics (macrokinectics) were performed by studying cell population growth kinetics of the tumor (microkinetics). In this manner the mathematical models derived were to describe the way in which the number of

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cells in a population increase; given the artifact of growth in cell culture, many scientists thought this process to be similar to bacterial growth. Bacterial growth is described by the simplest situation of population growth in which the rate of growth is constant and the logarithm of volume increases linearly with time.

$$dN/dT = kN \quad (1)$$

N = number of cells present at time +
dN/dT = change in cell number with time
k = growth constant

This equation may be solved by integration:

$$\ln (N_2 / N_1) = k (T_2 - T_1) \quad (2)$$

N_1 = number of cells present in the population at time T_1
N_2 = number of cells present in the populations at time T_2

Indicating that the growth (rate at which the number of cells in the population increases) is exponential.

Experimental growth is a simple direct growth model described by a constant growth rate with a geometric progression in which the doubling time does not vary over the entire period of the tumors' existence (5). It was commonly believed that tumor growth under "ideal" conditions was a simple exponential process terminated by the exhaustion of the nutritional support (5). Although it was reported in the 1960's that exponential growth of tumors was only observed rarely and for relatively brief periods of time (5).

A convenient value or term that expresses the specific rate of growth of a population is the doubling time (or generation time). The doubling time is defined as the time required for the number of cells in the population to double during growth. In terms of tumor growth it would be the time required for the volume to the tumor to double its size. Since the most convenient and easy index of tumor growth rate of a subcutaneous solid tumor is usually measured from serial Vernier caliper measurements or for internal tumors, serial radiographs have been used (6). This is a fairly difficult task while working with laboratory animals.

Also it is wise to utilize just one observer through a series of measurements since experimental tumors may vary considerably in their firmness (6), diametric measurements can vary much depending on how much pressure is applied when measuring.

Tumor volume may not necessarily be the best indicator of the amount of live neoplastic tissue since regions of necrosis can eventually make up a large part of the tumor volume. Although it is probably the most appropriate indicator since it is a non- invasive method (does not required the tumor to be removed) and can be followed per time. For a viable cell count of the tumor this can only be obtained directly by excision of the tumor (6).

Interestingly it has been observed that tumors grow more and more slowly as the tumor gets larger (5) with no appreciable period of growth at a constant specific growth rate. This would be the type of growth rate that would be expected for a simple exponential growth model. This continuous deceleration of growth makes the diameter of a solid tumor when plotted against time, a close approximation to a straight line (7). In most cases tumor growth is smoothly curvilinear on a semi log plot throughout the observed growth period. This implies that a specific growth rate for tumors is usually not only variable even for a short time but that it decreases steadily.

While the search for a comprehensive equation for tumor growth is still ongoing, models that fit wide ranges of data pertaining one type of tumor (considering the basic biological mechanisms involved) have been attempted with certain success. Tumor growth has been described more suitably by the Gompertz function (2,5). According to which the time required to double the tumor mass increases accordingly to an exponential function. Although the Gompertz equation provides a more accurate description of the early phase of the tumor growth process; (what can be considered to be quasi-exponential) it limits the growth of a tumor to fit the equation. In spite the fact that 2/3 of the Gompertzian curve will be able to fit many different tumor kinetic curves, there is still 1/3 of the growth curve of many tumors that will not fit the Gompertzian equation. This flaw might be due to irregular growth patterns exhibited by the tumors that may incorporate plateaus or dominant periods separated by Gompertzian growth Spurts (8).

$$W/W_o = e^{A(t)}$$
$$A(t) = A(1-e^{-at}) \quad (3)$$

W = tumor size at any time (t)
W_o = initial tumor size
A and a are constants

Nevertheless the Gompertzian curve seems to fit the earlier phase of tumor growth, the initial doubling time of the Gompertz curve is not a good descriptor of the early phase of the growth rate. For it depends upon the choice of time zero (which is often arbitrary in most models). The doubling time at the point of the first volume measurement depends on when the observer decides to start measuring and in the accessibility of the tumor. Also in the Gompertz equation, the possibility of introducing errors when extrapolations are extended far beyond the measured data is highly increased. This can occur mainly because changes in tumor size can change the equation of tumor growth.

In summary, computations utilizing the Gompertz function fit experimental tumor growth data better that previously used simpler functions. We consider it is a vast improvement over the earlier utilized exponential function model, nevertheless this Gompertz function can

still be improved. In addition, two problems with the Gompertz equation that should be pointed out is that the early exponential phase of tumor growth is not accounted for accurately. Also the Gompertz equation has a pre-assumed maximum volume, which in reality may or may not be attained.

In the model utilized in our laboratory, human breast carcinoma cell lines (MDA-MB231) transplanted in vivo (athymic nude mice) it is of ultimate importance that our derived mathematical parameters be independent of the number of passages of the cell line or tumor in question.

We are proposing a mathematical model for the MDA-MB231 human breast carcinoma growing in vivo (athymic nude mice); in which tumor cells proliferate by a modified exponential process similar to the Gompertzian function. In this model successive doublings occur at increasingly longer intervals. This new proposed model results because of the inability to reconcile differences between Gompertzian kinetics and our observed tumor growth findings. We propose a model that utilizes a function that can fully describes and fit in-vivo data. In our model, cells are regarded as multiplying exponentially but their net accumulation is subjected to retarding factors as for example cell loss (9). It was mentioned earlier that other causes may produce growth-delaying effects, but since most of these parameters are measurable; they will permit us to describe tumor growth kinetics with certain confidence. Our equation as previously mentioned entails three parameters. Albeit human tumors transplanted to nude mice have been reported to have a good approximation with the Gompertz function (11); our function provides even better means of describing human breast tumor transplants growing in vivo. Our model is based on the known fact that tumors grow in different ways and makes a successful attempt to fit the data with a function that allows flexibility in growth behavior.

$$W/W_o = e^{\alpha(t)}$$

$$\alpha(t) = a_o + a_1 t + a_2 t^2 + \ldots = \sum_i a_i t^i \quad (4)$$

W = tumor size at any time (t)
W_o = initial tumor size
a_i's are constants

Our model uses a polynomial fitting equation obtained with the help of the kin fit program of the Department of Chemistry at Michigan State University. Reliable measurements of tumor growth curves were used in enough tumor numbers over sufficient amount of time. Our model in contrast to the Gompertz curve does not pretend to extend the data far beyond what has been measured neither does it introduces a plateau for growth.

Growth kinetics of four human breast carcinomas was comparable when studied in the nude mice (11). This finding suggests that other human breast tumor types growing in vivo might as well be comparable to our describe model.

Resumen

Se han propuesto muchos modelos matemáticos para los parámetros de crecimiento de tumores en vivo. Sin embargo la mayoría de los modelos médicos han dado resultados variables, incluso cuando las condiciones experimentales son exactamente iguales. Existen un sin numeros de factores que son capaces de afectar el crecimiento del tumor y que se deben tomar en cuenta al proponer un modelo matemático para el crecimiento del tumor en vivo. Proponemos en este escrito un modelo para la cinética de crecimiento del tumor utilizando una función modificada de Gompertz que responde mejor al crecimiento característico de tumores en vivo.

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