MATHEMATICAL ANALYSIS OF CANCER CHEMOTHERAPY: THE EFFECTS OF CHEMOTHERAPEUTIC AGENTS ON THE CELL CYCLE TRAVERSE

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For the tumor model of Skipper and Zubrod, which has been analyzed previously for the theoretical FLM function and the effect of chemotherapy against tumors of known or assumed kinetic characteristics, the theoretical continuous labeling (CL) function is derived by considering an equivalent tumor (in terms of unlabeled cell populations) in which the density function of phase duration of cells in S-phase \( f_2(a_2) = \delta(a_2 - \infty) \) and the loss function \( L_2(t) = 0 \). This mathematical concept of blocking is applied to the analysis of synchronization in tumor growth and blocking effects in cancer chemotherapy. These effects of chemical agents on the cell cycle progression are being incorporated into a previously written computer simulation program for cancer chemotherapy. Whereas, a program is written and used to simulate the CL functions for L1210 leukemia, and primary and metastatic Lewis lung carcinoma.

Introduction. The cancer chemotherapeutic model system of Figure 1 deduced from Skipper and Zubrod's scheme of proliferative state in cancer (Skipper, 1969) has been analyzed mathematically (Chuang and Lloyd, 1975). In addition to the four consecutive proliferating phases \((G_1, S, G_2, M)\), the model comprises a compartment of resting cells \((G_0)\) and a compartment of dead cells \((D)\). Pharmacokinetics of anticancer drugs and cell–drug interactions at the tumor site are incorporated into the cell-cycle kinetic model in this kinetic study of cancer chemotherapy. A theoretical fraction labeled mitoses (FLM) function and the functions for the cell kinetics of the population...
distributed in the tumor mass during growth and multiple-dose, scheduled treatments have been derived based on the Von Foerster's population balance equation (Von Foerster, 1959) and the compartment equations. The kinetic equations and cell–drug interaction relationships are established for each proliferating phase and resting compartment to express their different responses to the drug treatment. In the analysis, the transit times of cells in the proliferating phases are assumed to be random variables with independently distributed probability density functions. The essential functional relationships are listed in the Appendix for a better understanding of the further developments in this paper.

The above mathematical model has been translated into computer language formulations (Chuang, 1975a). The computer program was written in Fortran IV for the PDP-15/76 equipped with a Cal Comp 565 plotter and allows for the simulations of scheduled treatments with cell-cycle specific, cycle nonspecific, and phase specific drugs. It includes three types of probability distributions—gamma, normal and lognormal distributions for the random phase durations of proliferating cycle and provides stepwise (linear, exponential, logistic and Michaelis–Menten type) variations of the involved kinetic parameters with respect to tumor size to enable itself to generate a Gompertzian tumor growth curve which is observed in most solid tumor systems. Two therapeutic systems of L1210 ascites leukemia treated by 1-β-D-arabinofuranosylcytosine (ara-C, NSC-63878) and solid Lewis lung carcinoma treated by 1-(2-chlorethyl)-3-(4-methyl-cyclohexyl)-1-nitrosourea (methyl CCNU, NSC-95441) are selected for the testing of the computer simulation program (Chuang, 1976). The results of each simulation are presented by a series of four plots which give pharmacokinetic information, expected cell populations and variations of kinetic parameters during growth or treatments. Also, the simulated FLM functions are compared to the observation data and served as a means of parameter verification.

However, some serious problems which contribute to eventual failure of chemotherapy, namely, the development of drug-resistant cells, host toxicity, some metastatic processes in pharmacologically protected compartments, and blocking effect by the drug, are not included in the previous modeling and simulation. The effects of chemical agents on mammalian cell cycle traverse have been investigated by Tobey and Ley (1971), and Tobey (1972). They observed that the entire population of cultured Chinese hamster cells grown in isoleucine-deficient medium accumulates in a state of $G_1$ arrest within 24 to 36 hours and, subsequently divides in synchrony by the adding back of isoleucine. Ara-C was found to inhibit DNA synthesis as well as to reduce grossly the rate of progression from $G_1$ into $S$. Some other investigators (Bertalanffy and Gibson, 1971; Graham and Whitmore, 1970; and Kim and Eidinoff, 1965) have also suggested the above inhibition, but conflicting results have been obtained