Chapter 15

Principles of Cancer Chemotherapy

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SECTION I: HISTORICAL PERSPECTIVE

Although the chemotherapy of cancer is a relatively recent development, it must not be forgotten that even before the 19th century efforts were made, using various metals including zinc, silver, and mercury, in an attempt to treat cancer, and some success was reported in folk medicine from the use of either metals or plant extracts such as colchicine. It was not until 1865 that Lissauer reported the beneficial effect of potassium arsenite in chronic leukemia. Although the use of metals did not return for more than 100 years, when the platinum compounds were successfully introduced into cancer chemotherapy, a concept was born which was strengthened by the successful use of chemotherapeutic agents, first against protozoa and later against bacteria.

The modern era of chemotherapy begins with the introduction of nitrogen mustard by Wilkinson in Great Britain and Gilman and Goodman in the United States. Significant clinical responses were obtained in patients with Hodgkin's disease, when for the first time it was shown that a chemotherapeutic agent could affect a malignancy which had become widely disseminated. Until then, surgery or radiotherapy were the only available treatments to localize disease, and once cancer had spread, the patient inevitably died. It must be said that *pari passu* with chemotherapy, the use of hormones was shown to be effective. Dodds synthesized stilbestrol and used it in disseminated prostatic cancer, and Hickman and Kendall

introduced cortisone for lymphoid malignancies in 1949. New derivatives of nitrogen mustard were synthesized by Ross at the Chester Beattie Institute in London, and melphalan, chlorambucil, and myeloran were introduced to clinical practice by Haddow, Galton, and others.

There still seemed no possibility of treating acute leukemia until the synthesis of the folic antagonist aminopterin by Seeger and the demonstration by Farber and his colleagues, in 1948, that it could produce remission in children with acute leukemia. These new substances, called antimetabolites, relied on an increasingly sophisticated knowledge of cell metabolism, and an ability to synthesize analogues of purines and pyrimidines. The work of Hitchings and Elion ushered in a golden age of chemotherapeutic development. Among the many antimetabolites produced, 5-fluorouracil (synthesized by Heidelberger) stands out as a drug that was specifically designed to treat carcinoma, and today remains one of the most effective agents available.

Advances in the knowledge of biochemistry led to some interesting attempts to exploit the biochemistry of the tumor cell. It was thought that the essential amino acid phenylalanine might enable a drug attached to it to gain easier entry to the cell. This was the reason for the synthesis of melphalan, and although the principle did not work, nevertheless a very useful chemotherapeutic agent was produced. The same was true of the compound cyclophosphamide, which is split by phosphatases present in high quantity in tumors. The high local phosphatase content was supposed to liberate the cyclophosphamide locally, and avoid damage to local tissues. Unfortunately this hypothesis was not borne out in practice, but nevertheless cyclophosphamide has remained an important alkylating agent. A number of other drugs were introduced by serendipity: plant, bacterial, or fungal molds became a source of a wide variety of important compounds, many effective antibacterial agents. Drugs such as actinomycin D, daunorubicin, and doxorubicin, were developed by an increasingly sophisticated pharmaceutical industry which was aware of the potential of these compounds as anticancer agents. Serendipity also came to the aid of the chemist, when (for example) extracts of the Madagascar periwinkle were being examined as a possible antidiabetic agent, and were shown to reduce the white cell count in rabbits. Inhibition of growth of tumor cells was noted, and the two compounds vinblastine and vincristine were extracted. These remain two of the most potent and widely used anticancer agents.

Along with the development of new agents came the realization of the best mode of their employment. Higher rates of response and more durable remissions could be obtained by using drugs in combination, particularly if the agents had different specific toxicities. Thus, while the antitumor effect summated, the toxic side-effects (which were the main disadvantage of chemotherapy) were limited. The highly successful MOPP regimen introduced by DeVita and his colleagues for the treatment of Hodgkin's disease, combinations of anthracyclines and alkylating agents for the treatment of childhood solid tumors, and the combination of platinum

compounds with bleomycin and etoposide, resulting in the cure of testicular cancer, are some examples of the successful use of curative combinations of drugs.

Although the history of chemotherapy is relatively short, major strides have been made towards the control of many previously fatal malignant conditions.

PHARMACOLOGY OF ANTICANCER DRUGS

Pharmacokinetic Principles

Before considering the main classes of anticancer drugs, it is necessary to review the principles by which these drugs achieve their effects, and the factors which govern their absorption, distribution, and excretion: their pharmacokinetics. Anticancer drugs, when administered orally, may be wholly or partially absorbed. Absorption may be influenced by a number of factors. The blood level of the drug then rapidly rises. During its passage through the liver it may undergo metabolic changes—so-called first pass metabolism—and various metabolites may start to circulate, being removed either locally or by excretion in the urine. In general, the blood level achieved will give an indication of the exposure of the tumor to the anticancer agent. The effective exposure will be a function of concentration

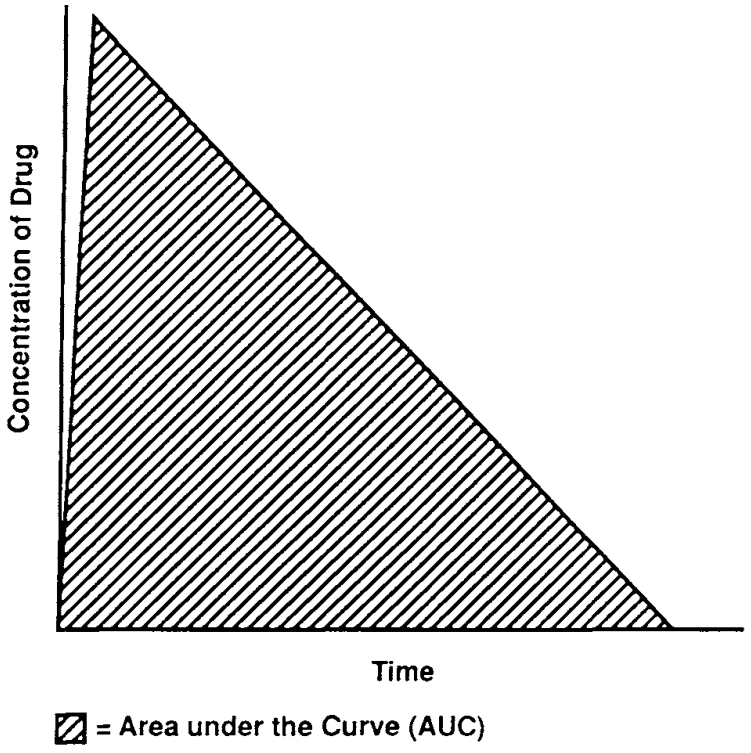

Figure 1. Curve showing variation of concentration of drug with time and derivation of the area under the curve (AUC).

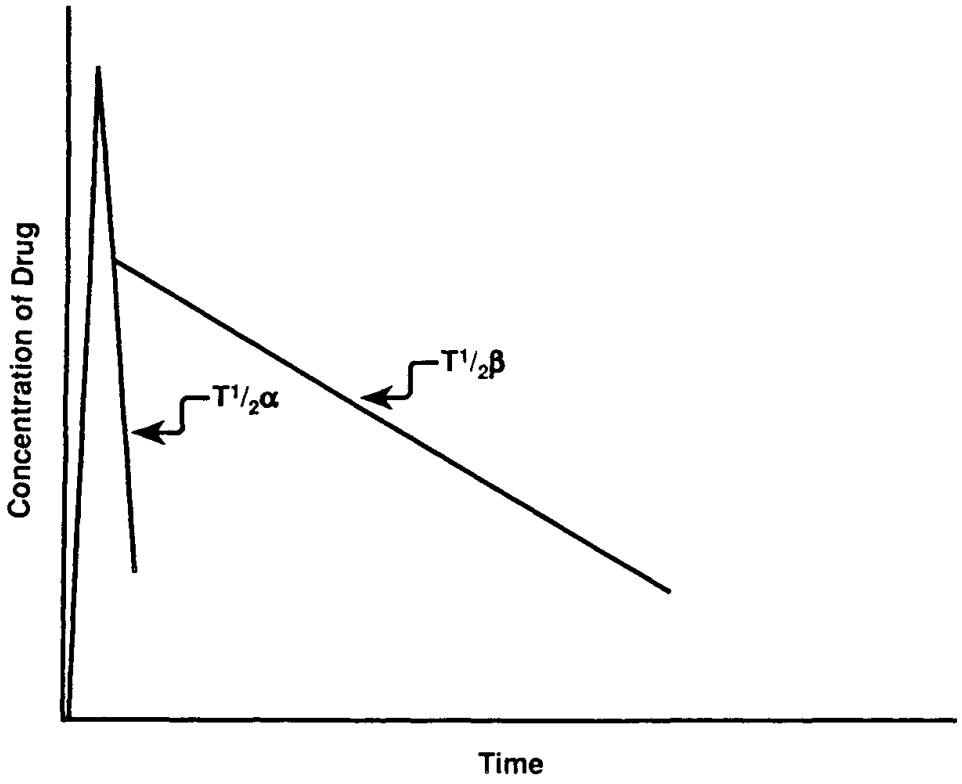

Figure 2. Curve showing variation of concentration of drug with time when drug enters two separate compartments.

multiplied by time. A typical exposure of a drug rapidly absorbed, uniformly distributed, and completely excreted, showing the curve for concentration and time, is given in Figure 1. The exposure of the tumor to the drug is measured by the area under the curve (AUC), and is shown in the shaded area in the figure. If the drug is distributed between two compartments, the curve of concentration in the blood will be modified (Figure 2). The rate of initial excretion is described as the time for half the drug to be excreted ($t^{1}/2\alpha$), and the time for the slower rate of excretion is $t^{1}/2\beta$.

Bioavailability of a drug is a frequently used term. This can be measured by assessing the AUC for the intravenously administered dose of the drug, and dividing this into the AUC for the same oral dose of the drug.

$$\text{Bioavailability} = \frac{\text{AUC for oral dose}}{\text{AUC for i.v. dose of drug}}$$

It can be shown that in the case of some drugs such as melphalan, an alkylating agent, there can be a wide variation in bioavailability, ranging from 10 to 50%, even within an individual. The same is true for 6-mercaptopurine and this may be of importance when long-term oral mercaptopurine therapy is being used for the treatment of childhood acute lymphoblastic leukemia.

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