Chemotherapy of Gynecologic Cancer

2nd Edition

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Editor

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This book is dedicated to Nina, Marc, Eric
and my parents with affection

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Foreword

The success of this monograph in its first edition offers testimony to the interest of gynecologic oncologists and other cancer specialists in the chemotherapeutic agents that can affect tumors of the reproductive tract in a palliative or curative manner. As knowledge in the basic oncologic sciences has accelerated explosively, so translation to patient care becomes increasingly complex with new cytotoxic agents and combinations thereof coming into clinical use almost daily.

This rapidly moving discipline is complicated further by the introduction of the concept of biologic modifiers and maturation agents that may impinge upon the chemotherapeutic picture. For all these reasons, the treatment of these malignant tumors is never static. Therefore, the care of life-threatening disorders wherein the primary therapist has the best opportunity for cure demands constantly advancing knowledge to remain at the cutting edge of modern treatment. Updating this monograph makes a valuable contribution to such patient care for cancer specialists of all persuasions.

SAUL B. GUSBERG, M.D., D.SC.

Foreword to the 1st Edition

The disciplines that utilize cytotoxic agents in their antitumor therapy have come into a new era: We have now the possibility of cure as well as palliation. Indeed, the past history of life extension with chemotherapeutic agents frequently posed a moral problem for the therapist, that of administering a harsh treatment that had the possibility of extending life for a brief period, but this was commonly interspersed with debility and pain for the subject together with emotional and financial disability for her family.

Current evidence indicates increasing rates of cure with chemotherapeutic adjuvants for many tumors, as new strategies are devised almost weekly and new anticancer drugs are introduced. Combination therapy, with surgery of irradiation therapy preceded or followed by chemotherapy, has become increasingly successful in eradicating disease, for the surgery or its equivalent can reduce the tumor burden, while the cytotoxic agents "mop up" so to speak. This should not be surprising for we know now that surgery or irradiation, no matter how radical, are local treatments while cancer is frequently a general disease. Only chemicals programmed to seek out the cancer cell and destroy it can be effectual in such instances.

Gynecologic oncologists are no strangers to this form of treatment for one of the earliest and most successful chemotherapeutic regimens has been that for choriocarcinoma. Those old enough to remember the total mortality of young women afflicted with this disorder can appreciate the change to almost total cure now available by cytotoxic agents. This dramatic change, unfortunately, has not as yet been seen in other advanced cancers of the female reproductive tract, where the past thirty years have brought more improvement from screening and early diagnosis than by treatment. However, recent advances have been made in the medicinal

treatment of gynecologic cancer and the era of formal training for gynecologic oncologists has accelerated its use and effectiveness.

Because new agents and new protocols of treatment are introduced continually, clinical trials have become the norm of advancing this form of therapy and gynecologic oncologists have frequently collaborated in this type of clinical investigation. The bewildering array of new agents and combinations has made it difficult for the generalist and even for the specialist to stay current. For this reason this volume, edited and authored by experts in special areas, will make an important contribution to the understanding and utilization of modern anticancer treatment. Gathering in this monograph the experience of many scholars and investigators is especially important for it presents the state of the art for gynecologic cancer treatment in the present, and a chemotherapeutic baseline for the future.

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I am especially indebted to the staff at Alan R. Liss who have had the task of bringing this edition to its final form. Additionally, I wish to express my appreciation to my office assistant, Jane Wittersheim, for all her help, support, suggestions, and especially for her patience in dealing with the individual authors and their manuscripts. I am also deeply indebted, as ever, to my colleagues, Vinay Malviya, M.D., John Malone, Jr., M.D., and Carl Christensen, M.D., Ph.D., at the Wayne State University School of Medicine and their secretary, Polly Decker, for their help, suggestions, support, and patience throughout this project.

A final personal tribute is due to my parents, Josef and Sophie Deppe, who have been my staunch supporters and best friends throughout my life and to whom this book is lovingly dedicated on the occasion of their 50th wedding anniversary.

Contents

Principles of Cancer Chemotherapy

Hyman B. Muss

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The explosive growth of oncology as a medical discipline, coupled with a rapidly expanding knowledge and technology of tumor biology, frequently obscures the humble and relatively recent beginnings of cytotoxic anticancer chemotherapy. In 1942 Gilman and coworkers [Gilman and Philips, 1946] treated a patient with lymphoma with nitrogen mustard and noted objective tumor regression. This historic event demonstrated the potential for cytotoxic agents to treat malignancies and began the modern era of cancer chemotherapy. Soon after, Farber demonstrated antitumor activity of the antifolate compounds in children with leukemia [Farber et al., 1948]. This was followed by the synthesis of methotrexate in 1949, which proved to be the first drug capable of curing an advanced malignancy, gestational choriocarcinoma in women [Hertz et al., 1961]. This latter event demonstrated conclusively that chemotherapy had the potential for curing human malignancy. The 1950s and 1960s were an exciting period of drug development, and by 1970 there were more than 20 active compounds available for cancer chemotherapy, including numerous alkylating agents, antimetabolites, antitumor antibiotics, plant alkaloids, nitrosoureas, and hormones. Such developments preceded another major milestone, the demonstration by DeVita and colleagues [DeVita and Serpick, 1967] that a combination of drugs (nitrogen mustard, vincristine, procarbazine, and prednisone; MOPP) used concurrently was capable of curing a majority of patients with advanced Hodgkin's disease. The importance of this achievement was the demonstration that the combination chemotherapy program could result in cure in at least one-half of the patients, while the same drugs used individually, although

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capable of causing objective responses, rarely resulted in cure. The success of the MOPP program stimulated interest in the development of combination chemotherapy trials for almost all types of human cancer and ultimately led to the development of curative programs in non-Hodgkin's lymphoma, childhood leukemia, Wilm's tumor, and testicular cancer.

The following chapter will introduce the reader to basic biologic and pharmacologic principles related to the use of cancer chemotherapy and will summarize the mechanisms of action, metabolism, and toxicity of the most commonly used agents.

CELL AND TUMOR BIOLOGY

Cell Kinetics and the Cell Cycle

Although cancer cells differ from the normal human cells from which they are derived, there are no unique attributes of cancer cells that distinguish them from their normal counterparts. Cancer cells generally do not proliferate faster than normal cells [Baserga, 1981], and both malignant and normal cells proceed through a specific series of steps or phases in the process of cell division. For broad purposes of classification, cytotoxic agents can be divided into two classes: 1) those that work exclusively or preferentially during a specific phase of the cell cycle (cell cycle specific) and 2) those that are able to induce cell death during any portion of the cycle (cell cycle nonspecific). The planning of single-agent and combination regimens and the optimal scheduling and sequencing of drugs rest on the knowledge of such cellular reproductive biology and drug-cell cycle specificity.

The specific phases of the cell cycle are illustrated in Figure 1. The cell cycle is divided into four unequal phases. During G_1, the intermitotic phase, cell machinery is primed for DNA synthesis. This phase is generally the longest phase of the cell cycle in mammalian cells but is highly variable in duration. The initiation and completion of DNA synthesis takes place during the S phase, which generally lasts 10–20 h. During this phase, normal 2N (diploid) DNA is copied in preparation for cell division. Following the S phase there is a short premitotic or G_2 phase lasting 2–10 h during which the machinery necessary for mitosis such as the spindle apparatus is synthesized. Finally, mitosis occurs during the M phase. During this very short phase, which generally lasts 30 min to 1 h, cells proceed through the four classic steps of mitosis: prophase, metaphase, anaphase, and telophase, resulting in cell division and the formation of two new daughter cells. New cells may then go back into cycle or become resting G_0 cells. While it is still difficult to quantitate the number

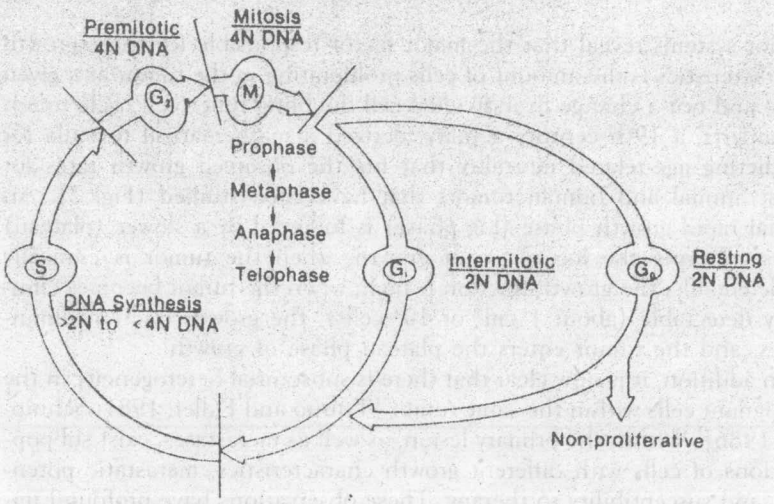

Fig. 1 The cell cycle. G_0, resting cells; G_1, intermitotic phase; S, DNA synthesis; G_2, postmitotic phase; M, mitosis; 2N, normal diploid number for DNA. Nonproliferative cells are not capable of reentering the cell cycle and will ultimately die.

of cells in the G_0 and G_1 phase, it is clear that in the majority of human solid tumors most cells are not actively cycling. Some of these noncycling cells may be incapable of proliferating and eventually die, while others may go back into cycle after spending variable amounts of time in the resting state. In addition, cells that are in cycle may be in any phase of the cycle at any given time. Thus, a cytotoxic agent that is specific for only one phase of the cycle might be expected to exert maximal effects only on a very small proportion of cells.

The growth of the tumor mass depends upon the percent of cells actively cycling (growth fraction), the cell doubling time (cycle time), and the rate of cell death. A tumor with a short cell doubling time, a large growth fraction, and a low rate of cell loss would be expected to increase in size rapidly, while one with a long cell doubling time, a small growth fraction, and a high rate of cell loss might grow only minimally over a long time interval. These factors are responsible for the great variability in clinical behavior that is frequently observed even in histologically similar lesions.

Most experiments in animal and human tumor systems have shown that tumor growth is most closely related to the proportion of cells that are actively in cycle and that the growth fraction is usually inversely related to the size of the tumor. Experimental data from a variety of

tumor systems reveal that the major factor responsible for these growth characteristics is the amount of cells proliferating in the tumor at a given time and not a change in individual cell doubling time (cell cycle time). Gompertz, a 19th century actuary, derived a mathematical formula for predicting age-related mortality that fits the observed growth rates for most animal and human tumors that have been studied (Fig. 2). An initial rapid growth phase (log phase) is followed by a slower (plateau) phase. During the log phase of growth, when the tumor is clinically undetectable, the growth fraction is high; when the tumor becomes clinically detectable (about 1 cm^3 or 10^9 cells), the growth fraction diminishes, and the tumor enters the plateau phase of growth.

In addition, it is now clear that there is substantial heterogeneity in the malignant cells within the same tumor [Tsuruo and Fidler, 1981; Schnipper 1986]. Within the primary lesion, as well as metastases, exist subpopulations of cells with different growth characteristics, metastatic potential, and susceptibility to therapy. These observations have profound implications not only for drug trials but also for the investigation of neoplasia in general.

These observations lead to the following conclusions:

1. Since most chemotherapeutic agents are effective in destroying proliferating cells, treating smaller tumors with their associated higher growth fractions should improve the therapeutic result.

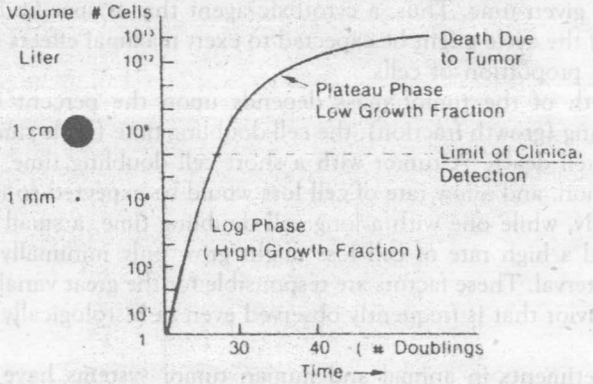

Fig. 2. Gompertzian curve. Size and number of cells in the tumor are plotted on the Y-axis; time and number of doublings on the X-axis. A period of increased growth, the log phase, is followed by a slower or plateau phase.

2. At the time of clinical detection (1 cm^3), a malignant tumor has already completed 75% of the doublings that it will need to destroy the host (33 of approximately 40).

3. Substantially decreasing the tumor volume ("debulking") whether by surgery, radiation therapy, biologic therapy, chemotherapy, or other treatment may enable one to improve therapeutic efficacy further by bringing resting (G_0) cells into the cell cycle (recruitment).

4. Within a given tumor there is likely to be cellular heterogeneity resulting in variable sensitivity of individual cells to specific agents.

The doubling times of several human tumors are shown in Table I. The concepts above are supported by the observation that cytotoxic therapy has had its greatest success in tumors with rapid doubling times and hence high growth fractions. Moreover, the extent and duration of remission are inversely related to tumor volume; patients with lower stage disease and smaller tumor volumes do best.

CONCEPTS OF CANCER CHEMOTHERAPY

Cancer chemotherapy is based on the following fundamental concepts:

1. For a given malignancy the potential for cure is inversely related to the tumor burden.

TABLE I. Tumor Doubling Time, Response, and Potential Curability With Chemotherapy[a]

Tumor type	Doubling time (days)	% CR to chemotherapy[b]	%Curable with chemotherapy
Gestational choriocarcinoma	1.5 (B)	85–100	75–95
Acute lymphoblastic leukemia	4–6 (H)	80–90	60
Testicular (excludes teratocarcinoma)	21 (S)	75	60
Hodgkin's disease	38 (S)	75	50–60
Squamous carcinoma	58 (C)	30–40	Rare
Lung—small cell	67 (T)	30–60	0–10
Adenocarcinomas	83 (C)	20–40	Rare
Lung—adenocarcinomas	134 (S)	20–40	Rare

[a] From B [Zubrod, 1972], H [Henderson and Jones, 1982], S [Shackney et al., 1978], T [Tubiana and Malaise, 1977], C [Charbit et al., 1972]

[b] CR = complete response.