

Clinical Cancer Chemotherapy Including Ambulatory Infusion



From the

LAHEY CLINIC FOUNDATION

Boston, Massachusetts

Edited by

ROBERT D. SULLIVAN, M.D.

Director, Department of Cancer Research

A voluminous and bewildering literature encompassing the preclinical and clinical areas of investigation in cancer chemotherapy has appeared in recent years, and new drugs are being introduced with alarming swiftness. Moreover, recent investigations of new dose schedules of currently available chemotherapeutic compounds and routes and duration of administration have added an element of unpredictability to the clinical investigations of cancer chemotherapeutic compounds. The plethora of dose schedules and techniques of drug administration described and the varied equipment used by different investigators further confuse an already perplexing problem.

CONTRIBUTORS

Leonard L. Anderson
Gerald J. Collins
Charles A. Fager
Lee Ingram
Amir M. Khazei
Paula Lestz
Khalil S. Nahra
Richard A. Oberfield
Yoichi Ojima
Ferris J. Siber
Rita Soule
Robert D. Sullivan
Neil W. Swinton
Kenneth W. Warren
Elton Watkins, Jr.
Robert E. Wise

CHARLES C THOMAS • PUBLISHER

Springfield, Illinois

Clinical Cancer Chemotherapy Including Ambulatory Infusion

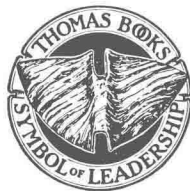
From the

Lahey Clinic Foundation
Boston, Massachusetts

Edited by

ROBERT D. SULLIVAN, M.D.

Director, Department of Cancer Research



CHARLES C THOMAS • PUBLISHER

Springfield • Illinois • U.S.A.

Published and Distributed Throughout the World by
CHARLES C THOMAS • PUBLISHER
BANNERSTONE HOUSE
301-327 East Lawrence Avenue, Springfield, Illinois, U.S.A.
NATCHEZ PLANTATION HOUSE
735 North Atlantic Boulevard, Fort Lauderdale, Florida, U.S.A.

This book is protected by copyright. No
part of it may be reproduced in any manner
without written permission from the publisher.

© 1970, by CHARLES C THOMAS • PUBLISHER
Library of Congress Catalog Card Number: 72-103590

*With THOMAS BOOKS careful attention is given to all details of
manufacturing and design. It is the Publisher's desire to present books
that are satisfactory as to their physical qualities and artistic possibilities
and appropriate for their particular use. THOMAS BOOKS will be true
to those laws of quality that assure a good name and good will.*

Printed in the United States of America
BB-14

**Clinical Cancer Chemotherapy
Including Ambulatory Infusion**

CONTRIBUTORS

Leonard L. Anderson, M.S.

Department of Cancer Research

Gerald J. Collins, B.S.

Department of Cancer Research

Charles A. Fager, M.D.

Chairman, Department of Neurosurgery

Lee Ingram, R.N.

Department of Cancer Research

Amir M. Khazei, M.D.

Senior Attending Surgeon and Oncologist

Veterans Administration Hospital

Manchester, New Hampshire

Former Associate Director

Department of Surgical Research

Paula Lestz, R.N.

Department of Cancer Research

Khalil S. Nahra, M.D.

Resident, Division of Colon and Rectal Surgery

Richard A. Oberfield, M.D.

Associate Director, Department of Cancer Research

Yoichi Ojima

Department of Cancer Research

Ferris J. Siber, M.D.

Head, Section of Nuclear Medicine and Radiologist

Department of Diagnostic Radiology

Rita Soule, R.N.

Department of Cancer Research

Contributors

Robert D. Sullivan, M.D.

Director, Department of Cancer Research

Neil W. Swinton, M.D.

Chief, Division of Colon and Rectal Surgery

Kenneth W. Warren, M.D.

Chairman, Department of General Surgery

Elton Watkins, Jr., M.D.

*Director, Department of Surgical Research
Chairman, Division of Research*

Robert E. Wise, M.D.

Chairman, Department of Diagnostic Radiology

*Dedicated to
Those Clinicians Whose Arduous Task
Is the Management of Patients with Cancer*

FOREWORD

A voluminous and bewildering literature encompassing the preclinical and clinical areas of investigation in cancer chemotherapy has appeared in recent years, and new drugs are being introduced with alarming swiftness. All these accomplishments, at such a rapid rate, require a quiet period to absorb the benefits thereof. Moreover, recent investigations of new dose schedules of currently available chemotherapeutic compounds and routes and duration of administration have added an element of unpredictability to the clinical investigations of cancer chemotherapeutic compounds. These isolated reports in the medical literature add to the problems plaguing the practitioner—rarely do they cite the specific indications for treatment or delineate the clinical situations and tumor types in which treatment may be of benefit. The plethora of dose schedules and techniques of drug administration described and the varied equipment used by different investigators further confuse an already perplexing problem.

The advent of the medical oncologist is one of the outstanding recent contributions to the management of patients with incurable cancer. Hopefully, he will coordinate the overall accepted measures for care of these patients. He should be concerned with the introduction and supervision of newer methods of cancer control as well as specific measures for the treatment of advanced forms of "solid tumors." He should integrate properly timed specific and nonspecific therapeutic measures and provide continuity of care, which may often be of incalculable value to the cancer patient. The import and ramifications of this burgeoning subspecialty are discussed. The multidisciplinary approach to the treatment of cancer is stressed.

It is not our intention to marshal our opinions but to attempt to provide some organization of the concepts of management of the patient with advanced cancer in respect to the specific methods of cancer control using systemic cancer chemotherapeutic agents. Special reference is made to protracted regional ambulatory infusion, drawing heavily from our own experience and the current practices of the Oncology Section of the Lahey Clinic Foundation. This symposium deals with the natural evolution of certain forms of cancer, the principles of systemic and regional cancer chemotherapy, a brief general survey of the chemical agents currently in use and their mechanisms of action and clinical applications, rationale of regional chemotherapy, techniques of treatment including catheter placement in various intravascular sites, maintenance of several types of infusion assemblies, conduct of infusion, complications of treatment, and the

results of therapy of various types of tumors in diverse anatomical sites. No attempt is made to cover the many pathophysiologic aspects of the management of the varied clinical problems presented by patients with different forms of cancer or the primary therapy of cancer. Furthermore, it is not within the scope of this symposium to review the fields of ablative or additive hormone therapy nor combined immunologic-chemotherapeutic programs.

This volume is directed toward the clinician who cares for a significant number of patients with neoplastic disease.

Grateful acknowledgment is made to Miss Charlotte R. Thompson of the Editorial Department, Paul D. Malone and Frank E. Steckel of the Medical Art Department, and George L. Buchanan of the Photographic Department for their assistance in the preparation of this book.

Robert D. Sullivan

CONTENTS

	<i>Page</i>
<i>Contributors</i>	v
<i>Foreword</i>	ix
<i>Chapter</i>	
1. THE MAGNITUDE OF THE CANCER PROBLEM—Results of Conventional Therapy, General and Regional Cancer Chemotherapy, and Adjuvant Chemotherapy <i>Robert D. Sullivan</i>	3
2. GENERAL CONSIDERATIONS IN CANCER CHEMOTHERAPY—Tumor Growth Rates <i>Robert D. Sullivan</i>	17
3. CARCINOMA OF THE GALLBLADDER, BILE DUCTS, PANCREAS, AND LIVER <i>Kenneth W. Warren</i>	29
4. THE NATURAL EVOLUTION OF COLORECTAL CANCER <i>Neil W. Swinton and Khalil S. Nahra</i>	37
5. CLINICAL PHARMACOLOGY OF ANTICANCER DRUGS—General Introduction <i>Robert D. Sullivan</i>	47
6. ALKYLATING AGENTS <i>Richard A. Oberfield</i>	55
7. FOLIC ACID ANTAGONISTS <i>Richard A. Oberfield</i>	69
8. CLINICAL PHARMACOLOGY OF PURINE AND PYRIMIDINE ANALOGUES <i>Robert D. Sullivan</i>	85
9. PROTRACTED HEPATIC ARTERY INFUSION OF 5-FLUORO-2'-DEOXYURIDINE—A Clinicopathological Study in the Dog <i>Amir M. Khazei and Elton Watkins, Jr.</i>	95
10. VINCA ALKALOIDS, ANTIBIOTICS, AND MISCELLANEOUS COMPOUNDS <i>Richard A. Oberfield</i>	105
11. CLINICOPHARMACOLOGIC STUDIES RELATED TO CANCER CHEMOTHERAPY <i>Leonard L. Anderson, Gerald J. Collins, Yoichi Ojima, and Robert D. Sullivan</i>	121

<i>Chapter</i>	<i>Page</i>
12. SURGICAL PROCEDURES FOR INFUSION OF HEAD AND NECK <i>Amir M. Khazei</i>	141
13. TECHNIQUES FOR INFUSION OF CHEST WALL AND UPPER EXTREMITIES <i>Amir M. Khazei</i>	155
14. TECHNIQUES FOR INFUSION OF PELVIS AND LOWER EXTREMITIES <i>Amir M. Khazei</i>	163
15. SURGICAL PLACEMENT OF ARTERIAL CATHETERS FOR TREATMENT OF CANCER OF THE LIVER, BILIARY TREE, AND PANCREAS <i>Elton Watkins, Jr.</i>	171
16. ANGIOGRAPHY IN ARTERIAL INFUSION CHEMOTHERAPY <i>Amir M. Khazei</i>	185
17. INFUSION HEPATIC ANGIOGRAPHY <i>Robert E. Wise</i>	191
18. DIAGNOSTIC VALUE OF SCINTILLATION SCANNING OF THE LIVER UTILIZING GOLD AU 198 AND ROSE BENGAL I 131 <i>Ferris J. Siber</i>	199
19. RATIONALE OF PROTRACTED ARTERIAL INFUSION THERAPY AND CONDUCT OF TREATMENT <i>Robert D. Sullivan</i>	209
20. THE ROLE OF AN ONCOLOGY NURSE ON A CHEMOTHERAPY SERVICE <i>Lee Ingram, Paula Lestz, and Rita Soule</i>	239
21. RESULTS OF PROTRACTED AMBULATORY INFUSION THERAPY—Evaluation of Response: Cancer of Head and Neck <i>Robert D. Sullivan</i>	249
22. INFUSION THERAPY OF PRIMARY BRAIN NEOPLASMS <i>Robert D. Sullivan, Charles A. Fager, and Yoichi Ohima</i>	265
23. RESULTS OF PROTRACTED AMBULATORY INFUSION THERAPY—Cancer of the Liver, Biliary System, and Pancreas <i>Robert D. Sullivan</i>	275
24. RESULTS OF INTRA-ARTERIAL INFUSION CHEMOTHERAPY OF EXTREMITIES, CHEST WALL, AND PELVIS WITH SPECIAL REFERENCE TO MELANOMA <i>Richard A. Oberfield</i>	291
<i>Name Index</i>	301
<i>Subject Index</i>	303

**Clinical Cancer Chemotherapy
Including Ambulatory Infusion**

Chapter 1

THE MAGNITUDE OF THE CANCER PROBLEM
Results of Conventional Therapy, General and Regional
Cancer Chemotherapy, and Adjuvant Chemotherapy

ROBERT D. SULLIVAN

Notwithstanding the many advances that have been made in the surgical management of malignant neoplastic disease and in the use of different forms of radiation treatment, cancer continues to be the second most common cause of death in the Western World and represents the third leading cause of hospital admissions of the middle-aged group in the United States.⁸ In 1900, cancer held eighth place as a cause of death. In 1950, it ranked second. There are several reasons why cancer has become a foremost cause of death: better diagnosis, more accurate reporting of causes of death, and control of communicable diseases which a generation ago took a heavy toll among young persons who now survive to the "cancer age." Fifty-five years ago only 16 percent of the population of the city of New York was more than 45 years of age. During 1967, almost 900,000 Americans were under treatment for cancer and more than 300,000 died. Although educational and research activities related to cancer have been vastly expanded, the number and rate of cancer deaths continue to increase. However, the ratio of patients who survive 5 years or more after treatment has improved from fewer than one in five 30 years ago to one in three today.³⁷ Exami-

nation of the mortality figures for cancer arising in different sites provides a perspective for evaluating the magnitude of the problem posed by patients with non-resectable or recurrent cancer. Table 1-I has been compiled from a review of the results of the treatment of cancer and survival data.^{3,4} Even in favorable types of cancer, the overall five-year survival rate is between 20 and 50 percent and in many common forms of cancer this figure is less than 5 percent.

There exists, then, a large group of

TABLE 1-I
OVERALL END RESULTS OF CANCER
THERAPY

Results	Five-year Survivals, Percent
<i>Favorable (20 to 50 percent)</i>	
Buccal cavity and pharynx	25
Larynx	35-40
Breast	28
Cervix uteri	20-40
Corpus uteri	40
Colon and rectum	25-30
<i>Unfavorable (5 to 20 percent)</i>	
Stomach	5
Prostate	8-27
Lung	5-10
Kidney and bladder	20-35
<i>Very Unfavorable (less than 5 percent)</i>	
Esophagus	0-5
Biliary passages and liver	0-5
Pancreas	0-5
Brain and nervous system	*

* Not established

patients with advanced cancer who are beyond cure or effective control with surgery or radiation treatment. These patients may indeed be incurable, but they are not untreatable. It is appalling to observe the aura of gloom and hopelessness that surrounds the patient with incurable cancer in respect to the attitude of the patient's family, his physician, and the nursing

staff. It emanates from the unjustifiable despair and inadequacy engendered by the feeling that "nothing can be done." There appears to be a vacuum of interest in the medical community. As a consequence, the patient who has advanced cancer is frequently neglected and fails to receive the incalculable advantages of proper nursing and medical care.

GENERAL MEASURES

Once the diagnosis of inoperable, advanced, or disseminated cancer is established by histological methods, the patient should be under constant and continuous medical management. When palliative treatment becomes necessary, it should be given promptly and adequately to alleviate symptoms and to forestall impending complications resulting from the inexorable and varied pathological dynamics of progressive cancer. The physician must never convey a feeling of rejection or resignation to the patient with advanced cancer. Emotional support of both patient and family with a warm and understanding relationship between patient and physician will do much to relieve the mounting anxieties and fears.

The problems of communication between the physician and the fatally ill patient and with his family are many and varied and, to some extent, controversial. Besides the purely medical aspects of the problem, there are often considerations derived from the religious, philosophic, and socioeconomic background of the patient. The knowledge of a life-threatening illness and impending death may occasionally be intolerable to a given patient. Although it is rarely necessary to tell the patient a blatant lie, this may be the only way to spare him unnecessary, prolonged agony.⁵⁰ However, this is a rare

circumstance; in most instances the patient is able to withstand the stress of gradual awareness of the gravity of his illness. Some physicians are reluctant to inform the patient that he has a malignant tumor and avoid completely discussion of the diagnosis and prognosis. This is a mistake as it keeps treatment entirely in an imaginary world by reinforcing denial mechanisms.

It is our practice to supply the patient gradually with sufficient knowledge of the seriousness of his illness as the situation requires. Since the patient is an important member of the "team" approach to therapy it is mandatory that he be aware of the nature of his illness and the related imminent problems. Since the word "cancer" is a fearful and terrifying word to many patients, we prefer to use the terms "tumor" and "growth." The patient is informed that he has an "incurable growth or tumor," that the condition is serious, and will probably affect his longevity, but that a treatment program will be instituted toward control and perhaps regression of the growth, accompanied by relief of current symptoms. He is advised to restrict his thoughts and worries to the day to day problems that develop rather than dwell upon the nonexistent problems that may occur in 6 or 12 months hence. He is made to feel a part of the "team effort" which

renders to him specific and nonspecific therapeutic measures. We have found that this approach—gradual enlightenment of the patient to a true awareness of his illness—will foster cooperation with his physicians and aid immeasurably in planning and carrying out treatment programs.

Usually the same philosophy and rules apply in communicating with family members as with the patient. As much knowledge and truth should be divulged as are compatible with the comprehension and emotional stability of the responsible relative and as the everchanging condition of the patient requires.

Many conditions associated with cancer can be corrected to make the patient more comfortable. Severe anemia can be treated by transfusion, and avitaminosis and undernutrition can be improved by dietary supplements. Certain disabling complications of progressive cancer may be relieved: hypercalcemia due to osteolytic bone disease or tumor elaboration of parathyroid-like hormone (treated with hydration and cortisone), intracavitary effusions (paracentesis and instillation of antitumor agents) and obstructive edema (salt restriction and diuretics) to cite a few of the endless medical problems that may occur in the cancer patient. Palliative surgery to remove foul and objectionable fungating masses or to relieve acute obstructions of the biliary, intestinal, or genitourinary tracts by reestablishing anatomic and functional continuity often provides added length of life and comfort to the patient. Coexistent but unrelated medical illnesses may be mistaken for manifestations of the known neoplastic disease; if unrecognized and untreated, they may produce crippling symptoms in a patient whose cancer is well controlled. Thus, the astute physician must constantly reevaluate and rediagnose the everchang-

ing pathological mechanisms in the cancer patient.

Cancer may produce pain in various ways, and the management of the pain in the patient with advanced cancer demands the utmost in skill and resource. Each patient with pain presents a problem that should be approached on an individual basis, and the psychological and physical factors contributing to the reaction to pain should be carefully assessed. Many of the emotional components of pain may have their basis in anxiety, fear, and anticipation of pain.²² Long-term efforts in managing pain caused by cancer must initially be directed to specific methods capable of causing tumor regression (for example, surgery, radiation, or chemotherapy) or to nonspecific methods capable of causing symptomatic improvement (for example, control of associated infection or relief of obstructed hollow viscera). When these methods are inappropriate, certain others may be considered: analgesic or neurotoxic drugs and neurosurgical procedures to alter the patient's perception of pain or to interrupt the neural pathways of pain. It should be emphasized that all methods to relieve pain, including drugs, have an appreciable number of undesirable side effects and should be utilized only after careful evaluation of the psychophysiologic makeup of the patient and his reaction to pain.

Analgesic drugs almost invariably are employed eventually in managing cancer pain. Narcotics continue to be the most reliable and effective drugs to control severe pain but should not be given until the effects of the less toxic antipyretic agents have been exhausted (such as aspirin or phenacetin). Tolerance and physical dependence with attending troublesome side effects eventually develop as a consequence of frequent and repeated adminis-

tration of narcotics but should not be the sole criteria for restricting their use in a given patient; rather, the relief of severe pain is the paramount consideration in the administration of these agents to patients with cancer.

Moreover, many of these patients may be candidates for the newer forms of specific cancer control introduced during the past two decades. Often the physician entrusted with the care of the patient who has advanced cancer is unaware of the nature or the availability of these newer, specific measures for the treatment of his patient and has long since relegated the patient to the hopeless category of a "terminal" case. For example, patients who have head and neck cancer, primary and metastatic liver cancer, advanced cancer of the gastrointestinal tract, and tumors of the brain and other sites are considered by many beyond the benefit of specific anticancer measures when they have exhausted conventional surgical and radiation treatments. Many of these patients may be candidates for systemic or regional chemotherapy and may derive temporary relief of symptoms with associated tumor regression and, in some cases, even prolongation of useful life. However, adding to the problems plaguing the practitioner is the prolific literature describing the use of new chemical agents and modification of techniques and methods of their administration. Rarely do these reports cite the specific indications for treatment or delineate the clinical situations and tumor types in which treatment might be of benefit. The plethora of dose schedules and techniques of drug administration described and the varied equipment used by different investigators add further confusion to an already perplexing problem.

At the present time, the main contribution of many internists to the overall care

of the cancer patient is limited to participating in diagnostic studies and referring the patient to the appropriate surgical or radiotherapeutic specialist. After it has been found that the cancer is incurable, the patient is returned to his physician who often feels inadequate to care for him. The internist's insecurity results from lack of knowledge concerning the natural evolution of the disease process and available treatment of even the more common cancers, such as breast, colon and rectum, and lung. The internist is in an exceptionally good position to care for such patients since he possesses wide knowledge in the areas of diagnosis, hematology, infectious disease, neurology, nutrition and metabolism, fluid and electrolyte balance, and so forth—areas to which problems of the cancer patient often relate.

Over the past one and a half decades, the internist-oncologist rightfully though belatedly has assumed much of this responsibility. The advent of the medical oncologist is one of the outstanding recent contributions to the management of patients with incurable cancer. Hopefully, he will coordinate the overall accepted measures for care of these patients. He should not be prejudiced by any single method of cancer control, for example, surgery, radiation therapy, or chemotherapy, since criteria of treatment are often fluctuating and not firmly established. For example, whereas in one country or institution or clinic the treatment for primary breast cancer is the most radical form of surgical removal, in other clinics, simple excision (or no excision) combined with radiation therapy is the treatment of choice. Data are not available at present to determine accurately the most effective forms of treatment of breast cancer; therefore, the oncologist must be receptive to new data and methods of treatment of