Chemotherapy of Cancer

CARTER/BAKOWSKI/HELLMANN

CHEMOTHERAPY OF CANCER

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CAUTION

The indications for and dosages of drugs and their combinations in this book have been taken from the world medical literature. The potential user of any of these drugs or regimes should however consult the original literature or see package inserts for use and dosage. Furthermore, the medications described do not necessarily have the specific approval of the Food and Drug Administration or any other countries' drug regulatory authority for use in the diseases and dosages for which they are recommended.

Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

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SECTION I

INTRODUCTION

CHAPTER 1

THE STRATEGY OF CANCER TREATMENT

Treatment Modalities

In the treatment of cancer one of the basic assumptions is that all malignant cells should be destroyed, removed or neutralized to achieve cure. Whether successful treatment has to eradicate all neoplastic cells or bring the cell number down to a level that can be controlled by the host's supposed immunologic defenses against the tumor is unknown at present. Five therapy modalities exist today which can be used in an attempt to bring about the requisite malignant cellular reduction: surgery, radiotherapy, endocrinotherapy, chemotherapy and immunotherapy.

As has often been stated, cancer is not one but a hundred different diseases each with its own natural history of spread, responsiveness to and failure patterns after various therapeutic maneuvers. For some tumors, a specific therapeutic procedure may represent the clear cut choice, while for others, a number of satisfactory alternatives may exist. This is true for most tumors and therefore optimal therapy is determined not only by the nature and extent of the disease, but also by the experience of the oncologists responsible for the patient's care and the facilities available for treatment.

Cancer can be classified into two major categories: solid tumors and hematologic malignancies. Solid tumors are initially confined to specific tissue or organ sites. In time, however, cancer cells break off from the original tumor mass, enter the blood or lymph system, reach distant parts of the body, and start secondary growths there (metastasis). When this occurs, the disease is in the disseminated stage. Conversely, hematologic malignancies involve the blood and lymph systems, and for this reason, they are frequently disseminated diseases from the very beginning.

In solid tumors, surgery and/or radiotherapy are the traditional, primarily chosen treatments. Neither modality, however, can be considered curative once disease has metastasized beyond the local

region (primary site and nearby lymph nodes) or has involved a vital organ extensively. Chemotherapy is relegated almost exclusively to secondary or tertiary treatment of solid tumors, i.e. when surgery and radiotherapy fail. Conversely, in hematologic malignancies, chemotherapy is the treatment of choice at diagnosis.

There are many approaches to treating a patient with cancer. Cancer is not a single disease but a multiplicity of diseases with variation being dependent on the organ system involved. Each type of cancer has its own diagnostic problems and its potential responsiveness to a wide range of therapeutic interventions. Each disease requires its own therapeutic strategy which is a unique blend of the various modalities available for usage. The development of this strategy requires a multidisciplinary input from surgical oncologists, radiation oncologists, medical oncologists and pathologists. For any given stage, of any given tumor type, the surgical oncologist offers the potential of more or less radical procedures. The radiation oncologist offers a range of new fractionation schedules and new delivery systems. The chemotherapist offers an endless mix of new drugs and drug combinations, while the immunologist offers a wide range of approaches to immune modulation. Clearly some priorities need to be set especially when one considers the unlimited numbers of interactions which can occur with combined modality studies. The priorities which have to be set should ideally be worked out within a disease-oriented strategy which takes into consideration the exigencies of the natural history of the disease under various classical therapeutic maneuvers.

Combined Modality Approach

One of the most important developments in the strategy of cancer treatment has been the full appreciation of the combined modality approach in adult solid tumor therapy (1). The pediatric oncologist has known for a long time the value of a multimodal therapeutic attack because of the results achieved in Wilms' tumor (2,3,4), embryonal rhabdomyosarcoma (5,6,7) and Ewing's sarcoma (8,9). This potential is now being appreciated by the clinical oncologist treating breast cancer (10,11) and other major cancer killers (12,13, 14).

Experimentally, the control of tumors requires eradication of the last neoplastic cell (15). Clinically it has been obvious for many years that surgical removal or radiotherapeutic ablation of

"localised" masses has not achieved the desired cancer control in a large number of patients. Oncologists have come to realize that many tumors which are apparently localized are in fact microscopically disseminated. We do not have the diagnostic tools to diagnose this, but recurrence proves that microscopic dissemination has taken place. Intensive study of the "natural history" of relapses after surgical or radiotherapeutic curative intent approaches has indicated groups in whom dissemination can be assumed to have occurred at the time of diagnosis in a large percentage of cases. Such groups include breast cancer patients with positive axillary lymph nodes, large bowel cancer cases with disease penetrating through the entire bowel and/or involving the regional lymph nodes, and all curative resection gastric cancer, pancreatic cancer and lung cancer patients.

If disseminated disease exists at the time of diagnosis then some therapeutic approach is needed which has the ability to control tumor cells anywhere in the body. Chemotherapy is at this time the master candidate for adjuvant usage to local therapy because of its proven cell kill potential in a wide range of human malignancies. As with surgery or radiotherapy, chemotherapy can be curative or palliative in varying degrees depending upon the individual tumor. By "cure" is meant that the life expectancy of the treated cancer patient is the same as "normal" life expectancy. Specifically, the same as that of a matched cohort in the general population. "Cures" from drugs alone have been obtained in such diseases as acute lymphocytic leukemia, Hodgkin's disease, diffuse histiocytic lymphomas, testicular cancer, choriocarcinoma and Burkitt's tumor (16). Chemotherapy achieves a high rate of objective tumor regression and enhanced survival in acute myelocytic leukemia, non-Hodgkin's lymphomas, multiple myeloma, adenocarcinomas of the breast and ovary and the chronic leukemias.

It has long been known experimentally that chemotherapy is more effective when tumor masses are small than when the tumor cell burden is high. The concept of first order kinetic cell kill by drugs (fixed percentage kill rather than fixed number kill per effective dose) means that, with a small tumor burden, total cell kill can be achieved with a reasonable number of repetitive doses which with a large tumor cell burden would still leave residual cells which would eventually develop "resistance" and start to grow again. The assumption underlying the adjuvant chemotherapy trials of today is

that the drug regimens which can give objective regressions (greater than 50% shrinkage of measurable tumor mass) in advanced diseases will be able to achieve total cell kill when applied to the microscopic residual disease remaining after surgical removal of the great mass of tumor bulk. The possibility that this assumption may be valid is borne out by the preliminary results of Fisher and Bonadonna (10,11) in breast cancer and the results of Jaffe and Cortes (17,18) in osteogenic sarcoma.

The utilization of immunotherapy as an adjuvant to surgery and/or radiotherapy rests on many of the same assumptions outlined for chemotherapy. The critical differences between immunotherapy and chemotherapy at this point in time within the framework of this strategy are as follows: (a) Immunotherapy is postulated to kill tumor cells by zero order kinetics (fixed number); (b) immunotherapy is postulated to be able to control only small cell numbers, therefore, (c) regression of advanced disease cannot be utilized as a predictor for adjuvant choice; (d) the correlation of tests, which measure immune response enhancement with immune modulation, and tumor cell control is still not established; (e) the question of disease specificity with various tools for immune modulation remains to be established.

As we attempt to develop our therapeutic strategies the importance of adequately staging all patients is easily evident. We need to strive for total international agreement on staging approaches and staging nomenclatures so that we can correlate the massive data which are being reported each year. We need to approach each tumor with clinical staging initially and pathologic staging wherever possible. The conflicts between clinical and pathologic staging systems need to be resolved recognizing that each tumor will have to be staged with an individualized mix of clinical and pathologic technique as available within the location patterns of spread for each type.

We are in an exciting period of therapeutic research in which the potential to increase the control rate of major tumor types is high. If we are to fulfill this potential we will need to develop even more fully the multidisciplinary input to disease-oriented strategy. No longer can any therapeutic modality isolate itself and claim certain tumors and stages for their own. Multimodal cooperation will be the routine of the future.

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