

Recent Advances in Cancer Chemotherapy

ROBERT B. DIASIO, MD

Associate Professor of Medicine and Pharmacology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

The present status of cancer chemotherapy can be reviewed in light of selected basic principles with an acknowledgement of the role of established chemotherapeutic agents. Four chemotherapeutic agents recently approved for clinical use and their impact when used in combination regimens should be examined. Several important concepts influencing chemotherapy in the 1980s include the use of chemotherapy in the adjuvant setting, the use of hormonal receptor data in planning therapy, and the use of *in vitro* tests on tumor specimens to predict tumor sensitivity to cancer chemotherapy drugs (prior to administration of these potentially toxic drugs to a particular patient). Lastly the reader is cautioned about the potential of long-term complications with certain chemotherapy agents, especially in those patients who have had complete or extended partial remissions.

Review

The modern era of cancer chemotherapy began approximately 40 years ago when nitrogen mustard, a derivative of the mustard gases used in the World Wars, was demonstrated to cause regression of lymphomatous tumors initially in studies involving mice and later man. Since that time a variety of chemicals and natural products have been synthesized (or isolated) and subjected to various screening programs in an attempt to identify potential clinically-effective drugs. Today there are approximately 30 drugs that have been approved and deemed valuable in the treatment of various human cancers.¹ These agents can be categorized into six major classes (Table 1).

The development of these diverse agents

which effect various critical biochemical steps or processes has occurred during a period in which there have been rapid and significant gains in our understanding of the molecular biology of the cell. Concomitantly, there has been an increased understanding of tumor cell biology which has markedly influenced the way cancer chemotherapy drugs are used today. Cell kinetic studies in animal models have demonstrated that a single malignant cell can multiply within a host animal to eventually kill the host. Thus curative therapeutic approaches must aim to eradicate every malignant cell. Studies with anticancer agents in animal models have shown that chemotherapy kills cells in a first-order kinetic manner, *ie*, with each treatment a constant percentage (rather than a constant number) of cells is killed. These generally accepted "principles" have provided support for the aggressiveness now used in many of the multiagent chemotherapy regimens and have formed the basis for adjuvant and maintenance chemotherapy.²

Multiagent, or combination chemotherapy, the major approach used in advanced cancer today, has been influenced by a better comprehension of the cell cycle. Thus it is recognized that certain drugs act on cells only in a specific phase of the cell cycle (the life cycle through which a cell passes from its origin when formed from the mother cell to the point at which it in turn divides into daughter cells) while other drugs are non-cycle specific, being able to affect cells regardless of where they are in the cell cycle, including cells not actively replicating. The recognition of this concept has been utilized in designing effective combination regimens which aim at affecting cells in different

TABLE 1
Classification of Cancer Chemotherapy Agents

Alkylating Agents	
	Mechlorethamine (Mustargen)
	Cyclophosphamide (Cytosan)
	Chlorambucil (Leukeran)
	Melphalan (Alkeran)
	Triethylenethiophosphoramide (thiotepa)
Nitrosoureas	
	(BCNU or Carmustine)
	(CCNU or Lomustine)
	(5-(3,3-Dimethyl-1-triazene)-imidazole-4-carboxamide)
	(Dacarbazine or DTIC)
Antimetabolites	
	Methotrexate
	5-Fluorouracil (Fluorouracil, Adrucil)
	Cytosine arabinoside (ara-C or cytosar)
	6-mercaptopurine (Purinethol)
	6-thioguanine (thioguanine)
Antibiotic	
	Dactinomycin (actinomycin D. (Cosmergen))
	Mithromycin (Mithracin)
	Doxorubicin (Adriamycin)
	Daunorubicin (Daunomycin)
	Mitomycin C (Mutamycin)
	Bleomycin (Blenoxane)
Natural Products	
	Vinblastine (Velban)
	Vincristine (Oncovin)
	L-Asparaginase (Elspar)
Miscellaneous Agents	
	o,p'-DDD (Mitotane (Lysodren))
	Hydroxyurea (Hydrea)
	Procarbazine (Matulane)
	Cis-platinum diamine dichloride (Cisplatin, Platinol)
Hormones	
	Estrogens
	Androgens
	Progestational Steroids
	Adrenal Steroids
	Antiestrogen tamoxifen citrate (Nolvadex)

phases of the cell cycle to obtain the maximum therapeutic effect.

The success of chemotherapy in the management of human cancer can be seen in Tables 2 and 3.² Table 2 demonstrates that in at least seven tumor types, chemotherapy now offers either cure or at the very least a significant prolongation of life. While actual cure has not been achievable for the five tumors listed in Table 3, there nevertheless has been a demonstrated increased survival and palliation. For the remaining tumor types not listed, including the relatively frequent cancers such as carcinoma of the lung and large bowel, cure and palliation are less likely at present. With the development of new agents, it is hoped that more effective combination regimens will be created to improve survival in these currently less responsive tumors as well.

Update

Over the past several years there have been four new agents introduced clinically that are now not only approved for non-investigational use but also occupy important roles in cancer chemotherapy already. The increasing use of all four drugs necessitates a basic understanding of them by every physician participating in the care of a particular cancer patient.

Doxorubicin (Adriamycin)

Perhaps the most important new agent is Adriamycin. This drug and the closely related drug Daunorubicin (Daunomycin) are anthracycline derivatives obtained as fermentation products from *Streptomyces* (Fig 1). These

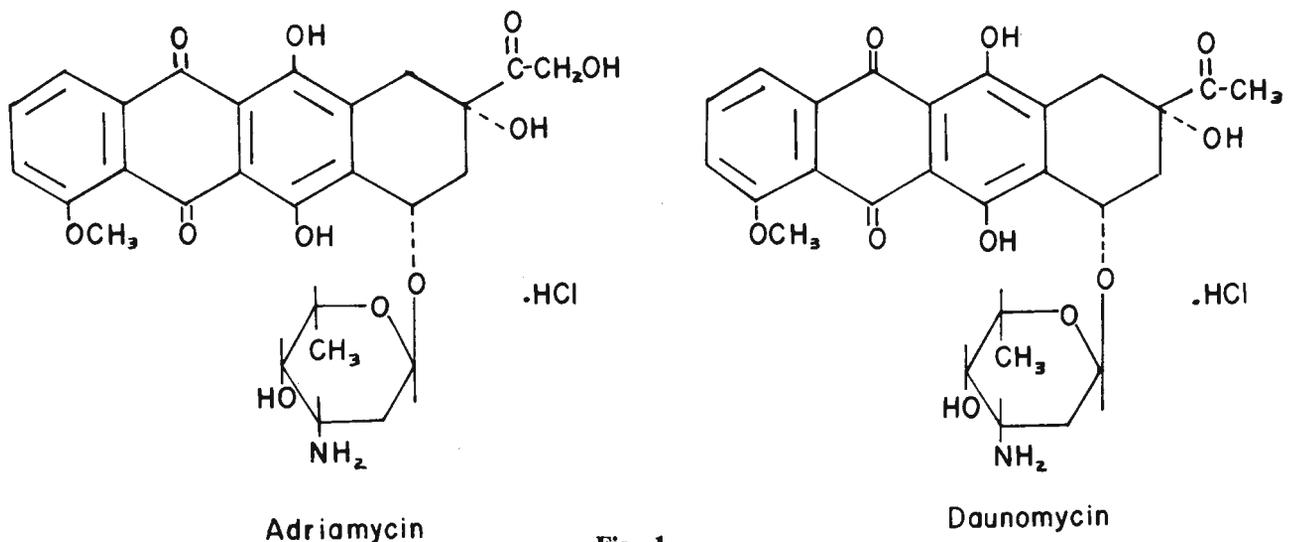


Fig. 1.

TABLE 2
Cure or Increased Survival

Type of Cancer	Chemotherapy	Results
Gestational trophoblastic tumors	Methotrexate, dactinomycin, vinblastine	70% cured
Burkitt's tumor	Cyclophosphamide (many others)	50% cured
Testicular tumors (nonseminoma)	Dactinomycin, Methotrexate chlorambucil, Bleomycin, Cis-platinum diamine dichloride	70-80% respond; 2-3% cured
Wilms' tumor	Dactinomycin plus vincristine with surgery and radiotherapy	30-40% cured
Neuroblastoma	Cyclophosphamide with surgery and/or radiotherapy	5% cured
Acute lymphoblastic leukemia	Daunorubicin, prednisone, vincristine, 6-mercaptopurine, Methotrexate, BCNU	90% remission; 70% survive beyond 5 years
Hodgkin's disease, stage IIIB and IV	MOPP, ABVD	70% respond; 40% survive beyond 5 years

(Note: Adapted from I H Krakoff, *Cancer Chemotherapeutic Agents, Ca-A Cancer Journal of Clinicians*, 27, 1977, 132.)
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drugs are classified as antibiotic cancer chemotherapy agents.

The mechanism of action of both drugs is believed to be via inhibition of DNA synthesis. These agents are known to interact with DNA, eventually intercalating into the nucleic acid helix leading to uncoiling of the DNA and inhibiting both RNA and DNA synthesis. Both agents are maximally effective during the S phase of the cell cycle, but inhibition can occur at all stages of the cell cycle, particularly at higher concentrations.³

The pharmacology of these drugs is still somewhat incomplete. At present they are used only intravenously. The major site of metabolism is in the liver by both soluble and microsomal enzymes. Less than 10% of the drug is excreted in the urine. Because of the importance of liver metabolism, the dose of Adriamycin is reduced in the presence of hepatic dysfunction. No drug adjustments are made for renal dysfunction. The total dose should not exceed 550-600 mg/M².^{2,3}

Both drugs have similar side effects and toxicities including: 1) gastrointestinal (nausea, vomiting, diarrhea, and stomatitis); 2) hematologic (leukopenia with a nadir at 10-15 days, and thrombocytopenia); 3) dermatologic (alopecia, local phlebitis and necrosis if extravasated); 4) cardiac (by far the most serious toxicity with these drugs is manifested as congestive heart failure due to a diffuse cardiomyopathy).

The major indications for Daunorubicin (Daunomycin) have been in acute granulocytic, and in lymphocytic, leukemia. In contrast, Doxorubicin (Adriamycin) has been active not only in leukemia but also in bladder cancer, breast cancer, bronchiogenic cancer, Hodgkin and non-Hodgkin lymphoma, thyroid cancer and sarcomas in general.

Bleomycin (Blenoxane)

Bleomycin, also of the antibiotic class of chemotherapy agents isolated from *Streptomyces*, is actually a mixture of several similar polypeptides, each having a molecular weight of approximately 1500. The A₂ peptide is the major compound present in the commercial preparation and is believed to be the active component (Fig 2).

The mechanism of action of Bleomycin appears to be by scission of double-stranded DNA, resulting in fragmentation of DNA, in turn causing inhibition of DNA synthesis. This drug appears to block cells at the G₂/M interphase of the cell cycle.

The pharmacology of this drug *in vivo* has been limited by the fact that the drug is a mixture of several compounds. Following administration, it disappears rapidly from the plasma with an estimated half life of 15-60 minutes. Since the drug is known to be excreted primarily via the kidneys, the dose should be reduced in the presence of renal dysfunction. Bleomycin is

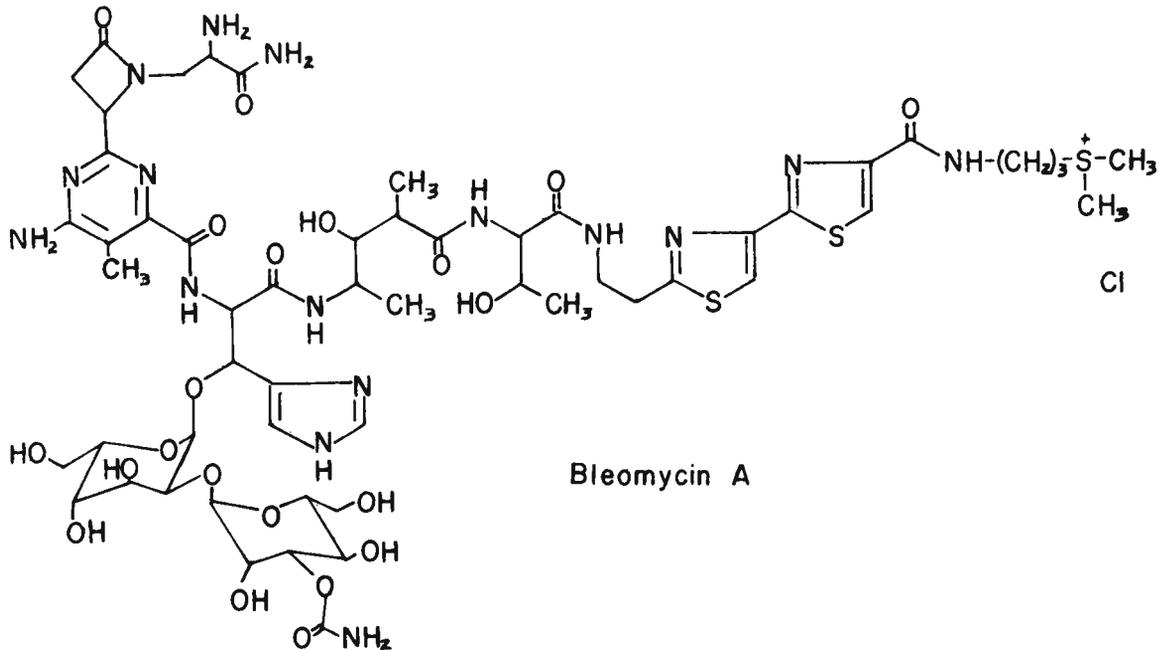


Fig. 2.

degraded mainly by the action of aminopeptidase which is present in tumor cells, liver and kidney. It is absent from the skin and lungs, two tissues which are particularly susceptible to damage from this drug. Bleomycin is administered either intravenously, intramuscularly, or subcutaneously.^{2,3}

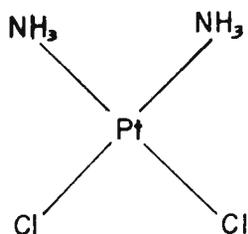
As noted above, Bleomycin toxicity includes skin toxicity (such as hyperpigmentation, thickening, ulceration, rash, alopecia, or nail changes) and pulmonary toxicity. This last severe toxic finding may be present as pneumonitis with dyspnea, rales and infiltrate progress-

ing to fibrosis. The occurrence of toxicity need not be related to the cumulative dose although it is more frequent with a total dose greater than 250 units/M² or a single dose greater than 25 units/M². The risk is increased particularly in individuals more than 50 years old who may have prior lung disease or may have previously been treated with radiation therapy. Pulmonary function tests have not been of value in predicting pulmonary toxicity. A cumulative dose of 400 units is the accepted maximum dose. Since the drug is a polypeptide, a potential side effect with this agent is anaphylaxis. Fever and chills

TABLE 3
Palliation and Prolongation of Life
Chemotherapy

<i>Type of Cancer</i>	<i>Chemotherapy</i>	<i>Results</i>
Prostate carcinoma	Estrogens, castration, cyclophosphamide	70% respond with some prolongation of life
Breast carcinoma	Androgens, estrogens, alkylating agents, 5-fluorouracil, vincristine, prednisone, Methotrexate, Adriamycin	60-80% respond with probable prolongation of life
Chronic lymphocytic leukemia	Prednisone, alkylating agents	50% respond with probable prolongation of life
Lymphosarcoma	Prednisone, alkylating agents	50% respond with probable prolongation of life
Acute myeloblastic leukemia	Cytosine arabinoside and thioguanine	65% remission with prolongation of life

(Note: Adapted from IH Krakoff, *Cancer Chemotherapeutic Agents*, *Ca-A Cancer Journal of Clinicians*, 27, 1977, 132.)
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cis-Diamminedichloroplatinum

Fig. 3.

occur in 20-30% of patients. The possibility of hypersensitivity is particularly a problem in lymphoma. Nausea and vomiting may also occur with administration of Bleomycin. One toxic manifestation notably absent with this chemotherapeutic agent is the lack of hematologic toxicity making this drug especially appealing for combination chemotherapy.

The major indications for Bleomycin have been in lymphomas (Hodgkin and non-Hodgkin), testicular tumors, and squamous cell carcinoma of the head and neck. Other indications are less clear at this time.

Cis-Diamminedichloroplatinum (Cis-platinum, Platinol)

This agent is a heavy metal coordination complex of platinum containing two ammonia groups and two chlorines in the Cis conformation (Fig 3). It is listed as a random synthetic type of chemotherapeutic drug. The mechanism of action appears to be through inhibition of DNA synthesis thought to result from both interstrand and intrastrand crosslinks in DNA. It appears to be cycle non-specific.

Cis-platinum is administered in an intravenous solution usually in an infusion from 15 minutes to eight hours. Following administration, plasma levels of the drug show a biphasic pattern of decay with an initial half life of 25 to 50 minutes and a terminal half life of 58 to 72 hours. Studies of distribution have demonstrated the greatest uptake in the excretory organs, ovary, and uterus. More than 90% of the platinum following administration is protein bound. Cis-platinum is excreted mainly via the urine. This drug should be used with caution or even withheld if renal dysfunction occurs with a

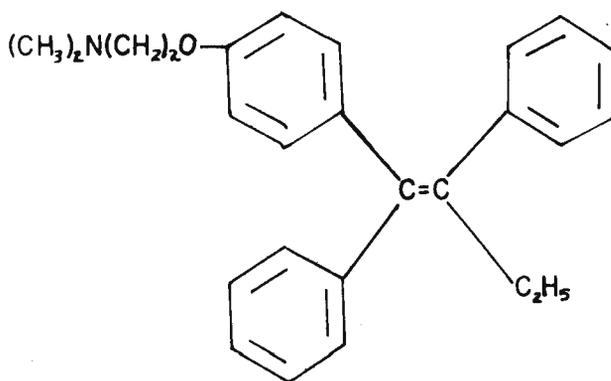
creatinine clearance of <60 ml/min. An attempt has been made to minimize renal toxicity secondary to Cis-platinum administration by hydrating the patient prior to drug receipt, giving diuretics and infusing chemotherapy slowly.

The renal toxicity appears to be dose related. Close follow-up of BUN, creatinine, and uric acid, and particularly creatinine clearance is advisable. Other side effects include ototoxicity, relatively frequent nausea and vomiting, leukopenia, thrombocytopenia, and anemia. Anaphylactic reactions have been described in no more than 1% of the patients given this drug. Peripheral neuropathies and loss of taste are less common side effects.⁴ This drug appears to be active in testicular tumors, ovarian cancer, bladder cancer, and head and neck cancer.

Tamoxifen Citrate (Nolvadex)

Tamoxifen is a synthetic non-steroidal triphenylethylene derivative that has been demonstrated to have potent anti-estrogen activity in several mammalian species. It is classified as a hormonal type of chemotherapy agent (Fig 4). The mechanism of action appears to involve inhibition of estrogen binding to cytoplasmic estrogen receptors present in sensitive cells such as breast cancer. It is believed that following binding to the receptor, estradiol-estrogen receptor formation is blocked. Since this receptor is necessary for activation of certain nucleic acid processes, the hormonal response of these cells is blocked.

This drug is given orally in 10mg tablets. Following oral administration, peak levels occur within four to seven hours. The initial half life is estimated to be from seven to 14 hours. Pro-



Tamoxifen

Fig. 4.

longed blood levels may therefore occur. This is thought to be due to concentration and excretion into the bile tract with reabsorption through the enterohepatic circulation.

Toxicity due to antiestrogenic actions include hot flashes, vaginal bleeding, menstrual irregularities, and pruritis vulvae. Non-specific gastrointestinal side effects have been described such as nausea, vomiting and distaste for food. Other toxic manifestations may include fluid retention, hypocalcemia, and dizziness.⁵

The major indication at present is in palliative treatment of advanced metastatic breast carcinoma. The use of this drug in estrogen-receptor positive premenopausal women with breast cancer is currently being evaluated by the National Surgical Adjuvant Breast Project.

New Combinations

The addition of these new agents has made possible new combinations taking into account not only the principle of cell cycle and cell kinetics suggested earlier, but also permitting modification of toxicity since many of these new agents have toxicity different from many of the standard agents in chemotherapy. For example, Bleomycin and Tamoxifen have essentially no hematologic toxicity and are attractive to use in combination with agents that might cause marked hematologic toxicity. Two particularly interesting new combinations include the ABVD regimen (Adriamycin, Bleomycin, Vinblastine and 5-(3,3-Dimethyl-1-triazene)-imidazole-4-carboxamide) used in Hodgkin disease and the Cis-platinum-Bleomycin-Vinblastine combination used in testicular cancer.⁶

The ABVD combination has been shown to be approximately equally active to the MOPP combination (Mechlorethamine+Oncovin+prednisone+procarbazine) used in the treatment of advanced Hodgkin disease. More importantly, there appears to be little cross resistance of the ABVD regimen with the MOPP combination making possible a suitable alternative treatment for MOPP failures. The combined use of Bleomycin and Adriamycin has also been shown to be active in some recent combinations used in non-Hodgkin lymphomas as well.⁷

In testicular cancers the contribution of these new agents (Bleomycin and particularly Cis-platinum) is even more impressive. While several active agents have been available for

many years including Methotrexate, Actinomycin D, and Mithramycin, the percentage of complete remissions was consistently 30% or less with no prolonged survivals. The combination of Cis-platinum-Vinblastine-Bleomycin has resulted in complete remission rates of 70% or greater with an increased percentage of prolonged survivors.⁸ The evolution of chemotherapy in the treatment of testicular cancer with first the addition of Bleomycin and later the addition of platinum illustrates the point made earlier that as new agents are introduced in combination with other effective agents, there is hope that still more effective combinations will be found in the treatment of other cancers as well.

Adjuvant Chemotherapy

Adjuvant chemotherapy is usually defined as the use of chemotherapy together with surgery and/or radiotherapy. As suggested earlier, cell kinetics provide a rationale for the use of adjuvant chemotherapy. Following removal of a tumor mass and a curative resection, the cell number should be reduced dramatically. When the cell number is relatively low, tumor cells are more likely to be actively growing and dividing. Since most chemotherapeutic drugs will kill cancer cells actively "in phase" in the cell cycle, it should follow that the smaller the tumor mass, the larger the growth fraction and the more likely the cells are to respond to cytotoxic drugs. The fact that only one cell is needed to theoretically kill the host, and the fact that chemotherapeutic drugs kill in a first-order kinetic manner, further supports the rationale for chemotherapy in the adjuvant setting. A number of experimental studies using mouse and rat tumor models have substantiated the value of adjuvant chemotherapy in prolonging survival.⁹

Clinical trials have now demonstrated a definite role for adjuvant chemotherapy in at least delaying the occurrence of metastases in premenopausal patients with breast cancer. It is still somewhat early to evaluate the overall effect on survival, although it does not appear to be as promising as originally hoped. Two regimens have been used in extensive adjuvant studies in breast cancer in this country and abroad. The American study has utilized the alkylating agent L-phenylalanine mustard, while the European study from Italy has utilized the combination of Cyclophosphamide, Methotrexate and 5-fluorouracil. Both studies have dem-

onstrated a definite role in premenopausal cancer, although the role in postmenopausal cancer is somewhat less clear.¹⁰

On osteogenic sarcoma there has been a dampening of the original enthusiasm for adjuvant chemotherapy. The initial regimens used during the past five years have included the use of Adriamycin with and without other agents and the use of high-dose Methotrexate. In these studies there has been the suggestion that again metastases may be delayed; but in this case it appears much less likely that any overall improvement of survival has resulted.⁹

For other tumor types the role of adjuvant chemotherapy at present remains much less clear. There is, however, the hope that with newer agents resulting in more effective combinations, there will be increased effectiveness of these drugs used early in the course of the disease with the anticipation that not only the onset of metastatic lesions will be delayed but also that survival time will be prolonged.

Receptor Status

Over the past several years there has been widespread acceptance by the medical and surgical community of the importance of obtaining breast tumor specimens at the time of surgery for assessment of estrogen as well as possibly other hormonal receptors.¹¹ The estrogen receptor assay has been shown to have a positive correlation greater than 65% with response to hormonal therapy in several large studies recently completed. Furthermore, patients with estrogen-receptor negative tumors appear not to respond to hormonal therapy. The most important impact of this receptor data is that approximately a third of all breast patients with metastasis are estimated not to respond to hormonal therapy. With the use of the hormonal receptor assays, patients who are estrogen-receptor negative may be spared ineffective therapy and may be begun on more effective cytotoxic chemotherapy at an earlier point.

Less clear is the importance of estrogen-receptor negative status in premenopausal patients. Recently it has been suggested in a retrospective study conducted at the National Cancer Institute that estrogen-receptor negative patients may actually respond better to chemotherapy than estrogen-receptor positive patients. This study, however, has been contradicted by yet another retrospective study. At

the present time prospective studies are needed to clarify this hypothesis, and no recommendations can be made.¹²

Prediction of Drug Response

For many years there has been the hope that one could test tumor cells, much as one tests bacteria cultured from an infected patient, thereby making a more rational choice of the agent or agents to be used. To some extent this approach has already been adopted in breast cancer where the presence or absence of estrogen receptors in the tumor specimen from a particular patient may determine whether hormonal therapy will be used. Recently a new method was demonstrated which permits tumor cells, obtained from specimens at the time of surgery, to be cultured so that drugs may be tested for possible effect. While only a limited number of cases have been studied at the present time, data in multiple myeloma and ovarian cancers suggest that the possibility exists that indeed a predictive test may be possible,¹³ thereby at the very least preventing the use of ineffective cytotoxic drugs and possibly determining effective drugs that may be used in the treatment of the individual patient. Again research will be conducted in the 1980s which will further clarify the usefulness of this new method.¹⁴

Long-Term Effects of Chemotherapy

While the immediate and idiosyncratic effects of the various chemotherapeutic agents have been well known, it is now clear that some of these drugs, particularly the alkylating agents and those drugs that intercalate into DNA, may result in the development of secondary neoplasms. These usually occur four to five years after the initial chemotherapy has been completed.¹⁵ The implication is that the very patients who have been "cured" by chemotherapy have then gone on to develop neoplasms secondary to the initial chemotherapy. This has now been seen in an increasing number of chemoresponsive tumors; eg with the use of alkylating agents in multiple myeloma or with alkylating agents with or without radiotherapy in Hodgkin disease.

The effects of radiotherapy have long been known to be associated with secondary neoplasms so that patients receiving radiotherapy and chemotherapy with agents which

interfere with the DNA structure may be especially at risk. With the development of more effective combinations, it is hoped that some of the agents responsible for these catastrophic toxicities may be removed and replaced by "non-carcinogenic" drugs.

Lastly, there will be a need to review the use of certain potentially "carcinogenic" agents in adjuvant regimens, especially in those patients who may indeed have been cured by surgery. With more experience it is hoped that the more toxic agents may be removed from these combinations as well.

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