CHEMOTHERAPY OF CANCER ◆6587

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INTRODUCTION

Cancer is one of the oldest diseases afflicting mankind, and the efforts at treatment have been recorded as long ago as the use of arsenic pastes in ancient Egypt. Today, cancer is second only to cardiovascular disease as the major cause of death in the United States. Each year an estimated 650,000 new cases are diagnosed and over one million known patients continue treatment. The major difficulties in mounting a rapid scientific assault on cancer are that it encompasses more than 100 clinically distinct diseases and is inextricably linked to fundamental life processes that still are not completely understood.

THERAPEUTIC APPROACHES

Several modes of therapy, including surgery, radiotherapy, and chemotherapy, are effective against cancer and have been developed to a point of practical use as either single or combined modalities. In many instances, cure can be achieved through removal or destruction of localized cancer, before it has spread to distant areas, by surgery and/or radiotherapy. Surgery is sometimes more successful when both the tumor and involved regional lymph nodes are excised. Radiotherapy is used to destroy localized tumors that are not accessible to surgery.

Unfortunately, although they may eradicate the primary disease, the local modalities often fail as a result of the spread of disease to other parts of the body. In such instances, the demonstrated capacity of chemotherapy for controlling disseminated disease offers the greatest hope for reducing mortality in a number of different cancers (1).

Like the other therapeutic measures, chemotherapy can be curative or palliative to varying degrees depending on the individual tumor (Table 1). "Cure" means that the treated cancer patient has a "normal" life expectancy, i.e. the same as that of a matched cohort in the general population.

Cures, or at least possible cures, by antitumor drugs alone have been achieved in such diseases as choriocarcinoma, Burkitt's lymphoma, acute lymphocytic leukemia, testicular cancer, and Hodgkin's disease. Chemotherapy combined with

Table 1 Chemotherapeutic potential in cancer

Effect of Chemotherapy	Cancer Type: Hematologic Malignancies	Adult Solid Tumors	Pediatric Solid Tumo
With optimal treatment, some patients survive free of disease for	Acute lymphocytic leukemia Advanced (stage III & usually IV) Hodgkin's disease	Trophoblastic carcinoma (choriocarcinoma) Testicular tumors	Wilms' Tumor[a] Ewing's sarcoma[a] Embryonal rhabdomyosarcoma
long periods	Burkitt's tumor		Retinoblastoma[a]
Significant number of patients achieve objective regression with survival gain	Non-Hodgkin's malignant lymphoma Multiple myeloma Acute granulocytic leukemia Chronic lymphocytic leukemia	Adenocarcinoma of the breast Adenocarcinoma of the ovary	Neuroblastoma[a]
Transient disease regression in some patients, but survival gain not established	Blast crisis of chronic granulocytic leukemia	Bronchogenic carcinoma GI adenocarcinoma Prostatic, bladder and thyroid carcinomas Soft tissue sarcoma Squamous cell carcinoma of the head and cervix Malignant melanoma	Osteogenic sarcoma

[a]Optimal use of chemotherapy requires combination with radiotherapy and/or surgery.

surgery and/or radiotherapy promises cure in many patients with childhood solid tumors such as Wilms' tumor, embryonal rhabdomyosarcoma, and Ewing's sarcoma. In other tumors, chemotherapeutic agents produce a significant degree of tumor cell kill that is reflected in a high rate of objective tumor regression and enhanced survival, although cure cannot be shown at present. These tumors include adenocarcinomas of the breast and ovary, non-Hodgkin's lymphoma, multiple myeloma, chronic leukemias, and acute granulocytic leukemia. In many of the other diseases, chemotherapy can achieve objective regression and palliative benefits in one fifth to one third of the treated patients.

Table 2 charts the drugs commonly used in the chemotherapy of the major types of cancer in the United States. The commercially available drugs considered useful in cancer therapy are listed in Table 3, together with their dosages and routes of administration, toxic effects, antitumor activity, and mechanisms of action. Table 4 details the experimental drugs that have shown definite antitumor effectiveness. All of the experimental drugs are usually available from the National Cancer Institute under the Food and Drug Administration regulations governing use of investigational drugs.

RECENT PROGRESS IN CHEMOTHERAPY

Since 1954, the National Cancer Institute has led a national effort to achieve chemical control of cancer. This systematic effort was undertaken by the government simply because its cost could not be met solely by private industry, the academic community, and independent clinical and laboratory institutions. The chemotherapy program area of the NCI encompasses every phase of drug research

and development, from the acquisition of potential anticancer agents through the completion of clinical trials and introduction of active drugs into medical practice.

Each year a large number of compounds are tested for possible antitumor activity. Most of these candidate agents are obtained from random sources, but an increasing number of rationally designed synthetic compounds are being examined as a direct consequence of recent advances in molecular biology. In 1972, the NCI evaluated 30,800 new compounds, including about 16,000 synthetic chemicals and 14,800 natural products derived from fermentation processes or plant and animal sources. During this period, tests in various animal tumors and in vitro cell systems increased 79% over those performed in 1971.

The qualitative and quantitative effects of experimental drugs in animal model systems are studied to establish effective dose levels and schedules of administration that will be applicable in the clinical situation. Similarly, investigations of drug toxicology are conducted to estimate safe dose levels for man and predict the toxic effects that may be encountered during clinical trials.

Over the years a large number of antitumor agents have been placed in clinical trial through the drug research and development program of the National Cancer Institute. The following have been among the most interesting drugs under investigation in recent years:

Adriamycin

This anthracycline antibiotic was isolated from a culture of *Streptomyces peucetius* var. *caesius* and, structurally, is a hydroxylated analog of daunorubicin (58, 59). Its mechanism of action is postulated as binding to DNA by intercalation between base pairs (60, 61) and inhibition of DNA and RNA synthesis (62, 63).

The experimental antitumor activity of adriamycin is superior to daunorubicin in L1210 leukemia (64) and P388 leukemia in mice (65), as well as in other systems such as Ehrlich ascites tumor and Sarcoma 180 in mice (66). Pharmacokinetic studies in mice and rats show that adriamycin is rapidly cleared from plasma; concentrated in the liver, spleen, kidney, heart, and lung; and excreted slowly in the urine and bile (67, 68). Alopecia, total depression of hematopoiesis, thrombocytopenia, blood coagulation changes, and hyperazotemia are the major organ toxicities in dogs and rabbits (69).

In man, adriamycin is rapidly cleared from plasma and slowly excreted in the urine and bile, being predominantly metabolized in the liver (70, 71). Data from over 2000 patients analyzed in the Cancer Therapy Evaluation Program of the NCI Division of Cancer Treatment (52) demonstrate significant objective response rates in a wide range of solid tumors, particularly adenocarcinoma of the breast (35%), malignant sarcomas (25%), and bronchogenic carcinoma (22%), as well as in malignant lymphomas (37%) and acute leukemias (25%).

Alopecia, myelosuppression, stomatitis, and nausea and vomiting are the most frequent toxic effects observed in man, but the most serious side effect is cardiac toxicity. This may be fatal if the total administered dose of the drug exceeds 550 mg/m^2 (72).

Table 2 Drugs commonly used for treatment of major types of cancer

Cancer Type	Primary Approach	Secondary Approach	Other Drugs with Reported Activity
HEMATOLOGIC MALIGNANCIES			
Acute lymphocytic leukemia	Induction: Vincristine sulfate + Prednisone Maintenance: Mercaptopurine Methotrexate with periodic use of "induction" regimen	Daunorubicin[a] Asparaginase[a] Cyclophosphamide Cytarabine hydrochloride	Thioguanine Carmustine[a]
Acute granulocytic leukemia	Cytarabine hydrochloride + Thioguanine	Daunorubicin[a]	Mercaptopurine Methotrexate Prednisone Cyclophosphamide Asparaginase[a]
Chronic granulocytic leukemia	Busulfan	Dibromannitol[a] Hydroxyurea	Mercaptopurine Melphalan
Chronic lymphocytic leukemia	Chlorambucil Cyclophosphamide	Prednisone	Cytarabine
Multiple myeloma	*Melphalan or Cyclophosphamide +* Prednisone	*Carmustine*[a]	*Chlorambucil*
Hodgkin's disease *(Stage III & IV)*	"MOPP" Combination: *Mechlorethamine (nitrogen mustard)* Oncovin (generic, vincristine sulfate) Procarbazine hydrochloride Prednisone	Vinblastine sulfate *Lomustine*[a] Bleomycin[a]	Adriamycin[a] *Dacarbazine*[a] Methotrexate Cyclophosphamide Chlorambucil Thiotepa Carmustine[a]
Non-Hodgkin's lymphoma	"COP" Combination: Cyclophosphamide Oncovin (generic, vincristine sulfate) Prednisone	*Adriamycin*[a] Bleomycin[a]	*Carmustine*[a] Procarbazine hydrochloride Methothrexate Vinblastine sulfate Chlorambucil Mechlorethamin[c]
Burkitt's tumor	Cyclophosphamide	Carmustine[a]	
Mycosis fungoides	Methotrexate		
Malignant insulinoma	Streptozotocin[a]		
Renal cell	Medroxyprogesterone	Vinblastine sulfate (poor) Lomustine[a]	Hydroxyurea (poor)
Malignant melanoma	Dacarbazine[a]	Carmustine[a] Vincristine sulfate	Cyclophosphamide Dactinomycin Chlorambucil Melphalan Hydroxyurea Thiotepa
Miscellaneous sarcomas	Adriamycin + Dacarbazine[a] Dactinomycin	Cyclophosphamide Vincristine sulfate	Methotrexate
Primary brain neoplasms	Carmustine[a] Lomustine[a] Dexamethasone (to control edema)	Vincristine sulfate Methotrexate	
PEDIATRIC SOLID TUMORS			
Wilms' tumor	Dactinomycin *Vincristine sulfate (with radiation and/or surgery)*	Adriamycin[a]	
Ewing's sarcoma	Cyclophosphamide *Dactinomycin* Vincristine sulfate (with radiation and/or surgery)	Adriamycin[a]	
Embryonal rhabdomyosarcoma	Cyclophosphamide Dactinomycin Vincristine sulfate (with radiation and/or surgery)	Adriamycin[a]	Thiotepa Methotrexate
Neuroblastoma	Cyclophosphamide Vincristine sulfate	Adriamycin[a]	Vinblastine sulfate Daunorubicin *Prednisone*
Retinoblastoma	Triethylenemelamine (+ radiation)		
Gestational trophoblastic neoplasms (choriocarcinoma)	Methotrexate Dactinomycin Vinblastine sulfate		

Table 2 (continued)

Cancer Type	Primary Approach	Secondary Approach	Other Drugs with Reported Activity
SOLID TUMORS			
Breast cancer	Diethylstilbestrol Testosterone Combination utilizing some or all of the following: Fluorouracil Methotrexate Vincristine sulfate Prednisone Cyclophosphamide	Adriamycin[a] Medroxyprogesterone	Lomustine[a] Vinblastine sulfate Thiotepa Ethinyl estradiol Fluoxymesterone Melphalan
Ovarian cancer	Melphalan or Cyclophosphamide	Fluorouracil Hexamethylmelamine[a]	Vinblastine sulfate Dactinomycin Methotrexate Thiotepa
Bronchogenic carcinoma	Mechlorethamine (nitrogen mustard) or Cyclophosphamide Methotrexate	Lomustine[a] Hexamethylmelamine[a]	Procarbazine hydrochloride Bleomycin+ Vincristine sulfate Thiotepa Adriamycin[a]
GI adenocarcinoma (large bowel, pancreas, stomach)	Fluorouracil	Carmustine[a] Lomustine[a] Cyclophosphamide	Mitomycin C[a]
Prostate	Diethylstilbestrol		Ethinyl estradiol
Squamous cell head and neck	Methotrexate	Fluorouracil Bleomycin[a]	
Squamous cell of cervix	Methotrexate Cyclophosphamide	Fluorouracil Bleomycin[a] Vincristine sulfate	
Endometrial carcinoma	Hydroxyprogesterone Medroxyprogesterone		
Adrenal cortical carcinoma	Mitotane		
Testicular seminoma	Melphalan		
Testicular carcinoma	Vinblastine sulfate Dactinomycin Mithramycin Bleomycin[a]		

[a]Available for investigational use only.

Different dose schedules have been used but, based on pharmacokinetic studies in man, a single dose of 60–75 mg/m^2 iv repeated every 3 weeks is recommended.

5-Azacytidine

This antitumor agent was isolated from a fermentation of *Streptoverticillium ladakanus* (73, 74) and independently synthesized by Piskala & Sorm (75). The mechanism of action has been elucidated in a number of studies (67–84). 5-Azacytidine is an analog of cytidine and is rapidly phosphorylated and incorporated in both RNA and DNA. By disrupting the processes of translation of nucleic acid sequences into protein, the synthesis of protein is inhibited. Moreover, it affects de novo pyrimidine synthesis by inhibiting orotidylic acid decarboxylase (85).

The drug has exhibited experimental antitumor activity against L1210 leukemia (86), lymphoid leukemia in AK mice (87), and Ehrlich ascites tumor in mice (88). Pharmacokinetic studies in mice show that 5-azacytidine is rapidly cleared from

Table 3 Commercially available cancer chemotherapeutic drugs

Drug	Usual Dosage	Toxicity: Acute	Toxicity: Delayed	Major Indications	Mechanism of Action
ALKYLATING AGENTS					
Mechlorethamine (nitrogen mustard; HN_2 Mustargen)	0.4 mg/kg, iv in single or divided dose	Nausea and vomiting	Moderate depression of peripheral blood count	Hodgkin's disease and other lymphomas, bronchogenic carcinoma	The alkylating agents act by transfer of alkyl groups to biologically important cell constituents such as an amino, carboxyl, sulfhydryl, or phosphate group, whose function is then impaired. Alkylation of the N^7 of guanine in DNA is one of the crucial reactions and leads to (*a*) alteration of guanine so that it forms an abnormal base pair with thymine (miscoding); (*b*) cleavage of the imidazole ring of guanine (destroying it); (*c*) linking of guanine pairs, producing cross-linked DNA strands which cannot replicate; & (*d*) depurination of DNA, causing actual breakage of the DNA strands (2-8).
Thiotepa (triethylenethiophosphoramide)	0.2 mg/kg, iv x 5 day	None	Bone marrow depression	Hodgkin's disease, bronchogenic & breast carcinomas	
Chlorambucil (Leukeran)	Start 0.1-0.2 mg/kg/day PO, adjust for maintenance	None	Bone marrow depression (anemia, leukopenia & thrombocytopenia) can be severe with excessive dosage	Chronic lymphocytic leukemia Hodgkin's disease, non-Hodgkin's lymphoma, trophoblastic neoplasms	
Cyclophosphamide (Cytoxan)	40 mg/kg iv in single or in 2-8 daily doses or 2-4 mg/kg/day PO for 10 day, adjust for maintenance	Nausea and vomiting	Bone marrow depression; alopecia; cystitis	Hodgkin's disease and other lymphomas, multiple myeloma, lymphocytic leukemia, many solid cancers	
Triethylenemelamine (TEM)	2.5-5 mg PO, 2 times weekly for 4 weeks initially	Nausea and vomiting	Bone marrow depression; alopecia; cystitis	Retinoblastoma	
Melphalan (l-phenylalanine mustard; Alkeran)	0.25 mg/kg/day x 4 PO; 2-4 mg/day as maintenance or 0.1-0.15 mg/kg/day for 2-3 weeks	None	Bone marrow depression	Multiple myeloma, malignant melanoma, ovarian carcinoma, testicular seminoma	
Busulfan (Myleran)	2-8 mg/day for 2-3 wks PO; stop for recovery; then maintenance	None	Bone marrow depression	Chronic granulocytic leukemia	
ANTIMETABOLITES					
Methotrexate (amethopterin; MTX)	2.5-5.0 mg/day PO; 0.4 mg/kg rapid iv daily 4-5 day (not over 25 mg) or 0.4 mg/kg rapid iv twice wk	Occasional diarrhea, hepatic necrosis	Oral and gastrointestinal ulceration; bone marrow depression (anemia, leukopenia, thrombocytopenia); cirrhosis	Acute lymphocytic leukemia, choriocarcinoma carcinoma of cervix and head and neck area, myccosis fungoides, solid cancers	Competitively inhibits dihydrofolate reductase, thus restricting the availability of tetrahydrofolic acid (THF) to cells. THF is critically important to metabolic transfer of one-carbon units in a variety of biochemical reactions.

Table 3 (continued)

Drug	Usual Dosage	Toxicity: Acute	Toxicity: Delayed	Major Indications	Mechanism of Action
					These include biosynthesis of thymidylic acid from deoxyuridine 5′-monophosphate (thymidylic acid is the nucleotide specific to DNA), and the biosynthesis of inosinic acid, the precurser of adenine and guanine *nucleotides in de novo purine* biosynthesis (9-11)
Mercaptopurine (6-MP; Purinethol)	2.5 mg/kg/day PO	Occasional nausea vomiting, usually well tolerated	Bone marrow depression occasional hepatic damage	Acute lymphocytic and *granulocytic* leukemia chronic granulocytic leukemia	Converted intracellularly to its *corresponding ribonucleotide* (6-thioinosinic acid), which may have several effects: *(a)* suppression of de novo purine biosynthesis via "pseudo-feedback inhibition" of the formation of ribosylamine 5-phosphate from glutamine & PRPP (5-phosphoribosyl-1-*pyrophosphate); (b) inhibition* of formation of adenylic and guanylic acid from inosinic acid; *(c)* inhibition of interconversion reactions among intermediate compounds in purine metabolism *(12-16)*
Thioguanine (6-TG)	2 mg/kg/day PO	Occasional nausea and vomiting usually well tolerated	Bone marrow depression	Acute leukemia	Is metabolized, along pathways similar to those of 6-MP to the nucleotide *structurally corresponding to guanine* and partially inhibits purine metabolizing enzymes. Its growth-inhibiting action seems to be substitution for guanine in nucleic acid synthesis, producing functionally altered polynucleotides.
Fluorouracil (5-FU; FU)	12.5 mg/kg/day iv x 3-5 day or 15 mg/kg/wk x 6	Nausea	Oral and gastrointestinal ulceration; stomatitis and diarrhea; bone marrow depression	Breast, large bowel, and ovarian cancer	Thymidylic acid is the deoxyribonucleotide of thymine (5-methyluracil), the pyrimidine base unique to DNA. Methylation of 2-deoxyuridine-5′-phosphate to yield this nucleic acid is ultimately catalyzed by thymidylate synthetase. 5-FU, when

Table 3 (continued)

Drug	Usual Dosage	Toxicity: Acute	Toxicity: Delayed	Major Indications	Mechanism of Action
					converted in vivo to the deoxynucleotide, has an affinity for the thymidylate synthetase system but is not itself incorporated into DNA. Thus, the primary cytotoxic action of the drug is to block thymidylate (and thereby DNA) synthesis. In addition, 5-FU is incorporated as the nucleotide into RNA, probably thereby depressing RNA synthesis directly by blocking incorporation of uracil and orotic acid into RNA (17–20).
Cytarabine hydrochloride (arabinosyl cytosine; Cytosar)	2–3 mg/kg/day iv until response or toxicity or 1–3 mg/kg iv over 24 hr for up to 10 day	Nausea and vomiting	Bone marrow depression; megaloblastosis	Acute leukemia	Originally proposed that inhibition is produced by phosphorylated derivative of *ara C* blocking conversion of cytidine diphosphate to deoxycytidine diphosphate. Later shown that tumor cell reductase is poorly inhibited by the di- or triphosphate (*ara*-CTP) of *ara C*. Most generally accepted is that *ara*-CTP inhibits DNA polymerase by competitive inhibition of deoxycytidine triphosphate rather than inhibiting polymerase synthesis (20–22).
NATURAL PRODUCTS (PLANT ALKALOIDS AND ANTIBIOTICS)					
Vinblastine sulfate (Velban)	0.1–0.2 mg/kg/wk iv or q 2 wks	Nausea and vomiting, local irritant	Alopecia; stomatitis; bone marrow depression; loss of reflexes	Hodgkin's disease and other lymphomas, solid cancers	Reversible mitotic arrest by binding drug to a cytoplasmic precursor of the spindle, probably during S-phase, and inhibition of RNA synthesis by effects on DNA-dependent RNA polymerase system. Vinca alkaloids also cause *rearrangement of binding sites in protein* of microtubular units in the mitotic spindle, permitting polymerization of protein to protofibrils (23–25).
Vincristine sulfate (Oncovin)	0.01–0.03 mg/kg/wk iv	Local irritant	Areflexia; peripheral neuritis; paralytic ileus; mild bone marrow depression	Acute lymphocytic leukemia, Hodgkin's disease and other lymphomas, solid cancers	

Table 3 (continued)

Drug	Usual Dosage	Toxicity: Acute	Toxicity: Delayed	Major Indications	Mechanism of Action
Dactinomycin (actinomycin D; Cosmegen)	0.015–0.05 mg/kg/wk (1–2.5 mg) 3–5 wk iv; wait for marrow recovery (3–4 wk), then repeat course	Nausea and vomiting, local irritant	Stomatitis; oral ulcers; diarrhea; alopecia; mental depression; bone marrow depression	Testicular carcinoma, Wilms' tumor, rhabdomyosarcoma, Ewings and osteogenic sarcoma, and other solid cancers	Dactinomycin forms a stable complex with DNA, producing inhibition of DNA-dependent RNA synthesis (26–29).
Mithramycin (Mithracin)	0.025–0.050 mg/kg q 2 day for up to 8 doses, iv	Nausea and vomiting; hepatotoxicity	Bone marrow depression (thrombocytopenia); hypocalcemia	Testicular carcinoma, trophoblastic neoplasms	Like dactinomycin, it inhibits DNA-dependent RNA synthesis without affecting DNA synthesis per se. It is thought to stablize secondary structure of DNA by forming bridges between complemenary strands of the helix (30).
OTHER SYNTHETIC AGENTS					
Procarbazine hydrochloride (Methyl hydrazine; ibenzmethyzin; Matulane)	Start 1–2 mg/kg/d PO; increase over 1 wk to 3 mg/kg; maintain for 3 wk then reduce to 2 mg/kg/day until toxicity	Nausea and vomiting	Bone marrow depression; CNS depression	Hodgkin's disease, non-Hodgkin's lymphoma, bronchogenic carcinoma	Uncertain. Exerts inhibitory effects on synthesis of protein, RNA, and DNA in cells in vitro. Its oxidative breakdown products degrade DNA in vivo. These derivatives may, in vivo, liberate formaldehyde, azomethine, N = hydroxymethyl derivatives, and hydrogen peroxide, which could produce the inhibitory effects. N-methylation of procarbazine occurs in vivo and a selective effect of the compound on methylation of transfer RNA could contribute to carcinostatic activity (31–35)
Hydroxyurea (Hydrea)	80 mg/kg PO single dose q 3 day or 20–30 mg/kg/day PO	Mild nausea and vomiting	Bone marrow depression	Chronic granulocytic leukemia	Directly inhibits DNA synthesis, primarily by inhibiting ribonucleoside diphosphate reductase. The effect is specific for the S-phase of the cell cycle (36–41).
Mitotane (*ortho para'* DDD; *o, p'* DDD; Lysodren)	6–15 mg/kg/day PO	Nausea and vomiting	Dermatitis, diarrhea; mental depression	Adrenal cortical carcinoma	Destruction of adrenal glands (42).
HORMONES					
Prednisone	10–100 mg/day PO	None	Hyperadrenocorticism	Acute and chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma,	The precise mechanism of hormones is unknown. Steroids must bind to cytoplasmic receptor proteins of tumor cells to exert

Table 3 (continued)

Drug	Usual Dosage	Toxicity		Major Indications	Mechanism of Action
		Acute	Delayed		
				breast carcinoma, multiple myeloma	antitumor effects. Loss of specific steroid-binding protein can be correlated with resistance to anticancer effects of certain steroids in breast cancer and lymphomas. Adrenocortical hormones injure specific cell types through unknown means. They interfere with lymphoid proliferation, cause dissolution of lymphocytes and regression of lymphatic tissue, and inhibit growth in certain mesenchymal tissues. The anti-inflammatory activity of adrenal steroids may be similar to their therapeutic action in certain tumors (43-47).
Diethylstilbestrol (DES)	1, 5 or 14 mg/day PO (1 mg in prostate)	None	Fluid retention; hypercalcemia; feminization; uterine bleeding; if during pregnancy, may cause vaginal carcinoma in offspring	Breast and prostate carcinoma	
Ethinyl estradiol (Estinyl)	3 mg/day PO	None	Fluid retention; hypercalcemia; feminization; uterine bleeding	Breast and prostate carcinoma	
Testosterone enanthate (Testosterone heptanoate)	600-1200 mg/wk, im	None	Fluid retention; masculinization	Breast carcinoma	
Testolactone (Teslac)	100 mg 3 x wk, im	None	Fluid retention, masculinization	Breast carcinoma	
Testosterone propionate (Oreton)	50-100 mg, im 3 x wk	None	Fluid retention; masculinization	Breast carcinoma	
Fluoxymesterone (Halotestin)	10-20 mg/day PO	None	Fluid retention; masculinization; cholestatic jaundice	Breast carcinoma	
Dromostanolone propionate	100 mg 3 x wk, im	None	Fluid retention; masculinization; hypercalcemia	Breast carcinoma	
Hydroxyprogesterone caproate (delalutin)	1 g im twice/wk	None	None	Endometrial carcinoma	
Medroxyprogesterone acetate (Provera)	100-200 mg/day PO; 200-600 mg twice/wk	None	None	Endometrial carcinoma, renal cell, breast cancer	

Drug	Usual Dosage	Toxicity		Major Indications
		Acute	Delayed	
Carmustine (bischloroethyl nitrosourea; BCNU) (48)	100 mg/m^2/day x 2 iv; not to be repeated for 6 wk	Nausea and vomiting; hepatotoxicity	Leukopenia and thrombocytopenia	Primary and secondary CNS neoplasms, Hodgkin's disease, multiple myeloma, malignant melanoma, GI adenocarcinoma, Burkitt's tumor, non-Hodgkin's lymphoma
Lomustine (cyclohexyl chloroethyl nitrosourea; CCNU) (48)	130 mg/m^2, PO, single dose repeated at 6 wk intervals	Nausea and vomiting; hepatotoxicity	Leukopenia and thrombocytopenia	Hodgkin's disease, primary and secondary CNS neoplasms, GI adenocarcinoma, bronchogenic carcinoma, renal cell
Hexamethylmelamine (49)	12 mg/kg/day x 21, PO	Nausea and vomiting	Bone marrow depression	Bronchogenic and ovarian carcinoma
Daunorubicin (daunomycin; Rubidomycin; Cerubidine) (50)	30–60 mg/m^2/day x 3 iv or 30–60 mg/m^2/wk, iv	Nausea, fever, red urine (not hematuria)	Bone marrow depression; cardiotoxicity; alopecia	Acute lymphocytic and granulocytic leukemia
Adriamycin (51, 52)	60–90 mg/m^2 iv, single dose or over 3 day; repeated q 3 wk	Nausea, red urine (not hematuria)	Bone marrow depression; cardiotoxicity; alopecia; stomatitis	Soft tissue, osteogenic & miscellaneous sarcomas, Hodgkin's disease, non-Hodgkin's lymphoma, bronchogenic & breast carcinoma
Bleomycin (53)	10–15 mg/m^2/wk or twice weekly, iv or im to total dose 300–400 mg	Nausea, vomiting, and fever; very toxic	Edema of hands; pulmonary fibrosis; stomatitis; alopecia	Hodgkin's disease, non-Hodgkin's lymphoma
Dacarbazine (DTIC; DIC) (54)	3.5 mg/kg/day iv x 10 repeated q 28 day	Nausea and vomiting ("flu-like" syndrome")	Bone marrow depression (rare)	Malignant melanoma, Hodgkin's disease
Streptozotocin (55)	1 g/m^2/wk iv x 4 continued if response is observed	Nausea and vomiting	Renal damage	Malignant insulinoma, carcinoid
Asparaginase (Elspar) (56, 57)	200 IU/kg/day iv x 28 day	Nausea, fever, and possible anaphylactic reaction	Hepatotoxicity; pancreatitis; CNS depression	Acute lymphocytic leukemia

[a]Experimental drug; not yet approved by the FDA and may be available only from the Investigational Drug Branch, Cancer Therapy Evaluation Program, National Cancer Institute. Dosage is tentative.

plasma, concentrates in lymphatic tissues, and is rapidly excreted in the urine as both unchanged drug and metabolites (89, 90). The pharmacokinetics in man indicate a plasma half-life of 3.5 hr after iv administration, with 85% of the radioactivity being excreted within 48 hr (91).

Phase I clinical studies established the maximum tolerated doses as 533 mg/m^2 iv single weekly dose, 160–200 mg/m^2 daily X 5 repeated every 3 weeks (92), and 1.6 mg/kg (60 mg/m^2) iv daily for 10 days (93). The principal toxic effects are severe nausea and vomiting, which are apparently dose related, and marrow suppression.

Although antitumor activity against solid tumors was originally reported (93), it does not appear to be confirmed in Phase II clinical trials (94). However, promising results are reported in the treatment of acute myeloblastic leukemia (95, 96) confirming the original reports from Czechoslovakia (97).

Bleomycin

This agent is actually a mixture of sulfur-containing glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus* (98). In the presence of sulfhydryl compounds, bleomycin binds to DNA and causes single strand scission (99, 100) which appears to be responsible for the inhibition of thymidine incorporation into DNA (101).

The drug has demonstrated antitumor activity against a number of experimental animal tumors including Ehrlich ascites carcinoma in mice, virus-induced tumors (102), and methyl cholanthrene-induced dermoid carcinoma transplanted intramuscularly in mice (103). While bleomycin is fairly active against a spectrum of experimental mouse tumors, including Lewis lung carcinoma, it has only minimal activity against L1210 and P388 leukemias. The drug accumulates in high concentration in skin and tumor tissue of experimental animals, as detected by measurements 30 min after iv administration (104). Similar findings of drug accumulation in skin and tumor tissue are reported in man, with urinary excretions of about 40% of the iv-administered drug in 24 hr (104).

The clinical data available to the Cancer Therapy Evaluation Program for 1174 patients treated with bleomycin reveals significant response rates in squamous cell carcinomas at various anatomical sites, malignant lymphomas, and testicular carcinoma (53). Drug toxicities include cutaneous reaction, stomatitis, alopecia, pyrexia, nausea and vomiting, and potentially fatal pulmonary fibrosis. However, the drug is remarkable in its lack of bone marrow toxicity even at very high doses. The most commonly used dose schedule appears to be 15 mg/m^2 iv twice weekly.

cis-Platinum (II) Diamminedichloride

This antineoplastic agent is one of a group of platinum compounds first noted to have antibiotic effect by Rosenberg and his colleagues, and since found to exhibit antitumor activity in animals (105–108). Structurally, it is a complex formed by a central atom of platinum surrounded by two chlorine or ammonia moeities in *cis*-position (107).

Although this compound inhibits incorporation of labeled precursors of DNA, RNA, and protein in mammalian cells in vitro (109), experiments in mice bearing Ehrlich ascites tumor cells indicate a selective inhibition of DNA synthesis (110). Interference with DNA synthesis is apparently caused by cross-linking of complementary strands of DNA (111).

The drug exhibits antitumor activity against a number of experimental systems, including B16 melanoma in mice, Walker 256 carcinosarcoma in rats (112), sarcoma 180 in mice (108), and DMBA-induced mammary tumors in rats (113). The selection of the drug for clinical studies stems from its significant activity in the L1210 system over a variety of ip dosage schedules. The drug has no activity by the oral route (Venditti, unpublished data of NCI).

cis-Platinum exhibits synergism in experimental tumors when combined with a variety of anticancer compounds including alkylating agents (114), pyrimidine and purine antimetabolites (115), ICRF 159 (116), and vinca alkaloids (115).

Pharmacokinetic observations in man show that platinum is rapidly removed from the circulation and widely distributed in the tissues. Less than 10% of the platinum remains in the plasma at 1 hr (117). The initial half-life ranges between 41 and 49 min, while the secondary one is between 58.5 and 73 hr (118). About 90% of the plasma radioactivity is protein bound; 19.2–33.9% and 25–43.6% of the administered drug is excreted by urine within 24 and 96 hr respectively (118).

Platinum has been used in Phase I clinical studies on various dose schedules: single iv dose repeated every 3 weeks (118, 119); daily iv dose X 5 days, repeated every 3 weeks (119, 120); and, daily doses by iv push until toxicity (121). The reported toxic effects include predictable and reversible myelosuppression, reversible renal insufficiency, high frequency ototoxicity detectable by audiometry, and GI intolerance. Phase II studies in major signal tumors are now in progress using either a high intermittent dose (50 mg/m2/day iv, repeated every 3 weeks) or 15–20 mg/m2/day iv X 5. Although some activity against malignant lymphomas and solid tumors was reported in the Phase I studies, it is too early to draw definite conclusions on antitumor activity in man.

Chromomycin A_3

This anticancer antibiotic of Japanese origin was isolated from a culture of *Streptomyces griseus* No. 7 (122) and is commercially available in Japan as "Toyomycin." Chromomycin A_3 is an aureolic acid analog consisting of an aglycone moiety (chromomycinone) and five attached pentoses (123–125). Studies of the mechanism of action show that Chromomycin A_3, in the presence of Mg^{2+}, inhibits DNA-dependent RNA polymerase (126–128). The interaction of the drug with DNA requires the presence of a guanine base (126, 127, 129). Inhibition of DNA polymerase has been demonstrated by Hartman et al (130).

The drug was selected for clinical trial on the basis of its activity against P388 leukemia in mice, where it shows superiority to both mithramycin and olivomycin. Cytostatic activity is also reported in a number of experimental animal tumors including Yoshida's sarcoma, Sarcoma 180, Ehrlich ascites, and others (131–133). Little activity has been reported against L1210 leukemia in mice.

Preclinical pharmacokinetic studies show that the drug is rapidly excreted in bile and urine, and almost totally cleared from the plasma in 3 hr after iv administration (134). Chromomycin A_3 has been used as a single agent in more than 500 Japanese and South African patients with a wide variety of neoplastic diseases (135, 136). Objective responses are reported in malignant lymphomas (137–141) and in solid tumors including bronchogenic carcinoma, GI adenocarcinomas, carcinomas of the female genital tract, malignant gliomas, and soft tissue sarcomas (139, 140, 142). The drug has also been used in combination with radiotherapy (140, 143) and with alkylating agents, where a synergistic effect is noted (144, 145).

Toxicity reported in Japanese and South African studies is surprisingly low, consisting of nausea and vomiting after daily doses of 1 mg or higher (139, 140), moderate leucopenia (137, 139, 140), and local reaction at the injection site with necrosis after extravasal administration. Recent Phase I studies in the United States reveal that renal toxicity is dose limiting when a daily iv dose for 5 days is escalated above 0.9 mg/m^2. Hypocalcemia, which has not been detected in previous studies, is also reported. Other dose schedules are now being explored and Phase II studies using lower doses are being proposed to avoid the dose-limiting side effects.

1,2-Di(3,5-dioxopiperazine-1-yl)propane

This compound, known as ICRF 159, was developed by the Imperial Cancer Research Fund facilities in London, England (146). Although the exact mechanism of action has not been fully elucidated, the cytotoxic effect occurs during late prophase and early metaphase (G_2-M) and involves inhibition of DNA synthesis (147, 148).

ICRF 159 was selected for clinical trials on the basis of antitumor activity in L1210 leukemia and in the Lewis lung system. The drug exhibits definite schedule dependency in L1210, where it is most active on an intermittent schedule and less active when administered daily. The most exciting data have been observed in the Lewis lung tumor which, when implanted in the flank of a mouse, metastasizes spontaneously to the lungs. Salsbury et al (149) examined this property of the tumor in a series of experiments comparing the ability of ICRF 159 and cyclophosphamide to prevent the metastases. ICRF 159 completely inhibited metastases formation at doses having little influence on the rate of growth of the primary tumor implant. Inhibition was produced by the effect of ICRF 159 on the development of blood vessels in the invading margins of the primary tumor. Cyclophosphamide did not prevent metastatic spread when used on schedules similar to ICRF 159 but did decrease the number and size of the metastases. All the untreated control mice developed metastases.

Initial clinical trials in Great Britain have been performed on a schedule of daily oral doses of 20–30 mg/kg/day in divided doses administered until the occurrence of hematologic toxicity (150–153). Leukopenia and thrombopenia occur within a few days of treatment initiation and are dose related (5 g total dose is the current British restriction). Dramatic decreases in the number of circulating blast cells are described in leukemia patients, and no cross-resistance to their antileukemic drugs has been noted.

Two studies with ICRF 150 have been completed in the United States (154, 155). Based on the pharmacokinetic study in man, the recommended dose for Phase II clinical studies is 3000 mg/m² po given once weekly. Phase II studies in the major signal tumors are in progress.

5(3,3-Dimethyl-1-triazeno)-imidazole-4-carboxamide (DTIC)

This drug is one of the new synthetic anticancer agents developed by the Division of Cancer Treatment of the National Cancer Institute (156–158). The postulated mechanisms of action include alkylating activity (159), inhibition of DNA synthesis, de novo purine synthesis, and SH interaction (160).

Experimental antitumor activity was originally reported against L1210 leukemia in mice (157) and is also seen in sarcoma 180, adenocarcinoma 755, and Ehrlich ascites carcinoma in mice (161). The drug does not appear to be schedule dependent (162) or cell cycle stage specific (163). Pharmacokinetic studies in man show a short plasma half-life and rapid urinary excretion by a renal tubular secretory mechanism. About 46% of the administered drug is excreted in 6 hr, 21% as DTIC, and 20% as AIC (5-amino-4-imidazole carboxamide), which is the final metabolite of the DTIC metabolic pathway (164–167).

Clinically, the drug is usually given in daily schedules, either 70–160 mg/m²/day X 10 repeated every 28 days or 250 mg/m²/d X 5 repeated every 21 days (54). However, high intermittent doses of 1050–1250 mg/m² repeated every 4–5 weeks have been reported (168). DTIC toxicities in man include bone marrow depression, nausea and vomiting, and a flu-like syndrome. Although the drug has been tested against various solid tumors, its most significant activity in man is in malignant melanoma. Data reported to the Cancer Therapy Evaluation Program reveal objective responses in 166 of 758 melanoma patients for a response rate of 22%, which is remarkable in its consistency throughout various clinical trials. The drug has been studied in combination with other active drugs in malignant melanoma and sarcomas.

1,3-bis(2-Chloroethyl)-1-nitrosourea (BCNU)

BCNU was the first of an exciting new group of compounds, the nitrosoureas, developed and clinically tested in studies sponsored by the Division of Cancer Treatment, NCI. It was synthesized, during the rational search for active congeners of 1-methyl-1-nitrosourea, as the twenty-third analog evaluated against L1210 leukemia in mice (169). Studies on the mechanism of action have shown alkylating activity by formation of a diazohydroxide and/or 2-chlorethylamine (170), selective interference with the utilization of histidine in 1-carbon metabolism through inhibition of formininotransferase (171), increased NADase activity and decreased concentration of tumor NAD^+ (172), and decreased DNA nucleotidyltransferase activity (173).

BCNU has antitumor activity against L1210 mouse leukemia (174), where it shows no schedule dependency for maximum activity and is equally effective as a single dose every other day for 8 doses, once every fourth day for 4 doses, or every

3 hr X 8 each fourth day for 4 courses. It is also active against intracranially implanted L1210 as well as leukemia L1798 and Dunning leukemia (175, 176).

BCNU has a wide range of effectiveness in a spectrum of other experimental tumors such as Wagner osteogenic sarcoma, Sarcoma 180, Ehrlich ascites carcinoma, Krebs II ascites carcinoma, and Taper ascites hepatoma in mice as well as Flexner-Jobling carcinoma, Jensen sarcoma, Yoshida sarcoma, Sugiura-Brown fibrosarcoma, and Iglesia's ovarian and adrenal tumors in rats (177). Moreover, it is also active against B16 melanoma, adenocarcinoma E0771, Ridgeway osteogenic sarcoma, and Sarcoma T241 (178).

Pharmacokinetic studies in experimental animals and man indicate that BCNU is rapidly metabolized; intact drug is not detected in body fluids shortly after administration. Studies with ^{14}C-labeled drug show prolonged levels of isotope in tissues of monkeys and man, probably representing radioactive fragments of the parent compound. DeVita et al (179) suggest that the breakdown products of the drug may be associated with its delayed toxicity. The radioactive compound is rapidly excreted by mice, suggesting biliary excretion and enterohepatic circulation, but the pattern of excretion is slower in both man and monkeys.

BCNU has received extensive clinical trial in a variety of tumors, and the compiled data of the Cancer Therapy Evaluation Program reveal high response rates in advanced Hodgkin's disease (75/149 = 50%), brain tumors (34/78 = 42%), multiple myeloma (12/31 = 39%), malignant melanoma (17/108 = 16%), and large bowel cancer (17/123 = 13%). In most cases, BCNU has been given at 200–300 mg/m^2 administered intravenously over 2–3 days. The current recommended dose regimen is 100 mg/m^2/day X 2 iv with courses repeated every 6 weeks.

Organ toxicities in man include delayed leukopenia and thrombocytopenia, nausea and vomiting, and hepatotoxicity. The few cases of pulmonary toxicity that have been reported to the Cancer Therapy Evaluation Program suggest that the effect may be drug related.

1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)

This agent was the first analog of BCNU selected for clinical studies because of its superior experimental activity in leukemia L1210 and great lipid solubility (48).

Unlike BCNU, CCNU has an asymmetrical structure which enables identification of its breakdown products (cyclohexylamine, cyclohexylisocyanate, and N,N'-dicyclohexylurea). Studies in L1210 ascites leukemia show that only CCNU or cyclohexylisocyanate prolong the S-phase to twice the normal period, while the other products are inactive (180). CCNU inhibition of DNA nucleotidyltransferase activity is about the same as that produced by BCNU (181). Recent studies on the binding of the breakdown products of ^{14}C-labeled CCNU reveal that radioactivity from cyclohexyl-labeled CCNU is extensively bound to proteins and not to the nucleic acids, while radioactivity from the ethyl-labeled CCNU is nucleic acid bound with only a fraction bound to proteins (182). These data suggest that CCNU interacts with proteins through cyclohexylcarbamoylation (183) and with nucleic acids by alkylation.

The antitumor activity of CCNU is superior to BCNU in L1210 leukemia, and it is also significantly active against Walker 256 carcinosarcoma in rats and B16 melanoma (48).

Pharmacokinetic studies in rodents show that 75% of the ^{14}C cyclohexyl- or ethyl-labeled CCNU is excreted in the urine in 24 hr after oral or ip administration, while about 10–20% of carbonyl- or ethyl-labeled CCNU is expired as $^{14}CO_2$ (184). CCNU is rapidly metabolized in dogs and monkeys and excreted predominantly in the urine (184). Pharmacokinetic studies with C^{14}-labeled drug in man show rapid metabolism, prolonged plasma half-life of radiolabeled compounds ranging from 16–48 hr, and urinary excretion of 50% of administered dose within 24 hr and 75% within 4 days with no parent drug detectable in the urine (185).

Clinically, clear superiority of CCNU over BCNU has been demonstrated in a controlled study of Hodgkin's disease (186) and activity is reported against malignant gliomas (187), gastrointestinal cancer (188), carcinoma of the breast, hypernephroma, bladder cancer, malignant melanoma, and squamous cell carcinomas in various anatomical sites. The toxic effects of CCNU include nausea, vomiting, and delayed leukopenia and thrombocytopenia (189). The recommended dose is 130 mg/m^2 (po), repeated every 6 weeks.

1-(2-Chloroethyl)-3-(4-methyl-cyclohexyl)-1-nitrosourea (Methyl CCNU)

This is a methylated analog of CCNU selected for clinical trial because of its superiority to both BCNU and CCNU in the advanced Lewis lung tumor in mice (48). The drug also has antitumor activity against L1210 leukemia by both the iv and oral routes.

Pharmacokinetic studies in man after single oral doses of either cyclohexyl- or chloroethyl-labeled methyl-CCNU show rapid absorption of both moieties of the parent compound, with significant plasma levels of radioactivity as early as 10 min after administration (190). The average peak plasma levels of radioactivity occur at 3 hr for the cyclohexyl moiety and at 6 hr for the chloroethyl moiety. These peak levels correspond to plasma concentrations of between 2 and 4 μg/ml of drug equivalence. The disappearance of radioactivity from plasma for the chloroethyl moiety is single phased with a half-life of 36 hr, while the cyclohexyl moiety disappears biphasically with an early exponential phase having a half-life of 24 hr, followed by a slower phase with a half-life of 72 hr. No parent drug is detectable in any plasma sample.

Phase II clinical trials of methyl-CCNU are proceeding in a number of institutions and cooperative groups. The data accumulated by the Cancer Therapy Evaluation Program for more than 300 patients indicate methyl-CCNU activity against adenocarcinoma of the colon, malignant gliomas, malignant melanoma, malignant lymphomas, and squamous cell carcinomas at different anatomical sites. However, the numbers are still small and more data are needed to confirm these findings.

The toxic effects of methyl-CCNU include nausea and vomiting at doses of 170 mg/m^2 or higher, and delayed bone marrow toxicity that is dose limiting (191). The recommended dose is 200 mg/m^2 po every 6 weeks with individual adjustment.

NEW DIRECTIONS IN CHEMOTHERAPY

Recently, the chemotherapy program area has been expanded and integrated into the Division of Cancer Treatment in the NCI under the new emphasis of the National Cancer Plan. The immediate objectives of the DCT program are to increase the number of patients responding to cancer therapy and prolong the length of the disease-free period of remission. The ultimate goal is the cure or control of cancer.

The increased scope of the DCT program includes not only the drug development and clinical testing aspects of the former chemotherapy program but also the improvement of therapy by combined modality approaches. These efforts will proceed largely on disease-oriented lines, with the major emphasis on effective treatment for the solid tumors that are the major cause of cancer deaths in the United States.

The major thrust in combined modality treatment will seek an integration of chemotherapy with surgery and/or radiotherapy, and perhaps with immunotherapy. This is a logical approach in view of the fact that chemotherapy is the only modality of unquestioned effectiveness against tumor cells found anywhere in the body. As pointed out earlier, chemotherapy, either alone or with other modalities, can cure some patients with at least eight different kinds of cancer.

The philosophic base of the combined modality approach is the recognition that surgery and radiotherapy have reached a plateau in their ability to cure solid tumors. These localized modalities kill tumor cells only where they are applied, and it is not technically feasible to increase the scope of their application for tumors in which they are effective. They fail to cure many patients, even when they remove all the tumor visible to the naked eye or diagnostic X-ray film. The reason for this failure is felt to be the presence of disseminated disease foci at the time of surgical excision of the primary tumor, which many times includes the surrounding tissue and part of the regional lymph nodes.

Chemotherapy, when used optimally, has the potential to eradicate these metastatic foci. The drug regimens that have shown the highest degree of activity in advanced disease will be the prime candidates for use in the combined modality approach. The degree of cell kill necessary to shrink a bulky solid tumor mass by greater than 50% is quite large. If this degree of cell kill could be directed against the relatively small tumor burden remaining after surgical excision, perhaps eradication of the last neoplastic cell can be achieved.

The major successes of chemotherapy have been in the hematologic malignancies, especially acute lymphocytic leukemia and advanced Hodgkin's disease. These triumphs of cure and long disease-free survival have not been translated to the common solid tumors, which are the major cause of cancer mortality in this country Many reasons have been put forth for this disparity of results, among them th differing kinetics of the tumors and the relative accessibility of the tumor cells t significant drug concentrations. One additional factor, which is often neglecte involves the point on the treatment strategy for a given disease at which chemoth apy is introduced.

As a general rule, the major potential for cure in any tumor lies in the initial therapeutic approach. In leukemia, a disseminated disease, chemotherapy is the treatment of choice at all stages of the disease (Figure 1). The optimum drug regimens are used in early disease, while new drugs or regimens are tried in later stages and the successful ones are integrated into the initial therapeutic approach. On the other hand, surgery and/or radiotherapy are the primary approaches in solid tumors without disseminated disease. Chemotherapy is relegated, almost exclusively, to secondary or tertiary treatment after the local modalities fail and the disease is advanced and disseminated. The secondary or tertiary treatment is rarely curative in any tumor, including hematological malignancies. It is understandable, therefore, that the chemotherapy presently used in solid tumors is not curative, although tumor regression, palliative benefit, and some survival increases are achieved. Any comparison of the results of chemotherapy in solid tumors and hematological malignancies should take into consideration the differences in the therapeutic approaches.

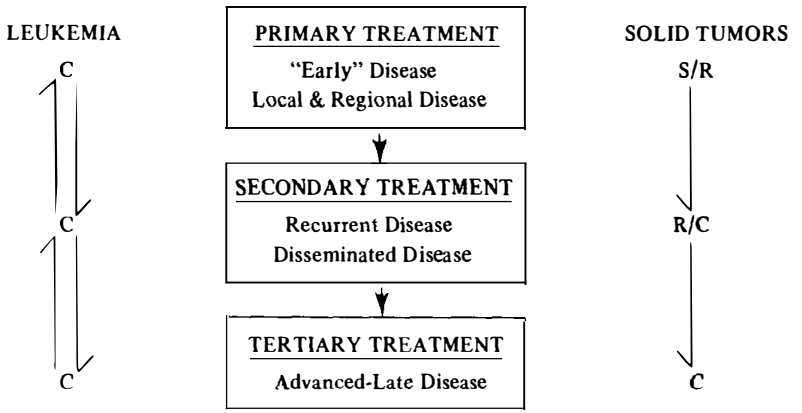

Figure 1 Comparison of therapeutic modalities in leukemia and solid tumors. C = chemotherapy; R = radiotherapy; S = surgery.

The proposed therapeutic strategy for increasing cure rates in solid tumors involves the integration of chemotherapy into combined modality approaches for primary treatment (Figure 2). In this scheme, new drugs or drug combinations would be tested in advanced disease and those showing positive results would be studied in the primary therapy of disseminated disease. An optimum regimen developed in this manner would then be integrated into combined modality treatment in local and regional disease.

Figure 3 outlines this type of approach to a therapeutic attack against breast cancer. The solid arrows show the standard flow of therapy, beginning with mastectomy and moving through hormonal manipulation and eventually to chemotherapy. The broken arrows indicate the concerted efforts of the NCI Division of Cancer

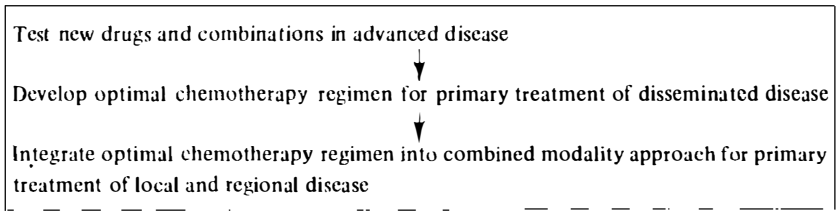

Figure 2 Proposed strategy for developing combined modality therapy for solid tumors.

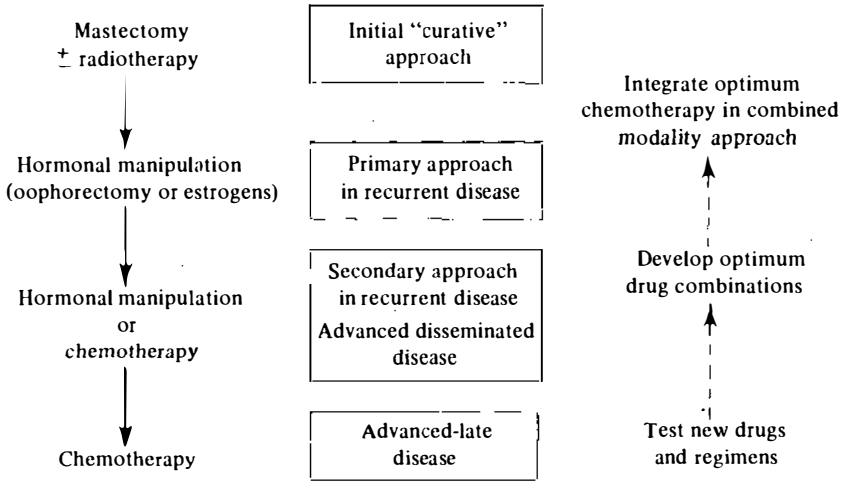

Figure 3 Proposed integration of chemotherapy into the treatment of breast cancer.

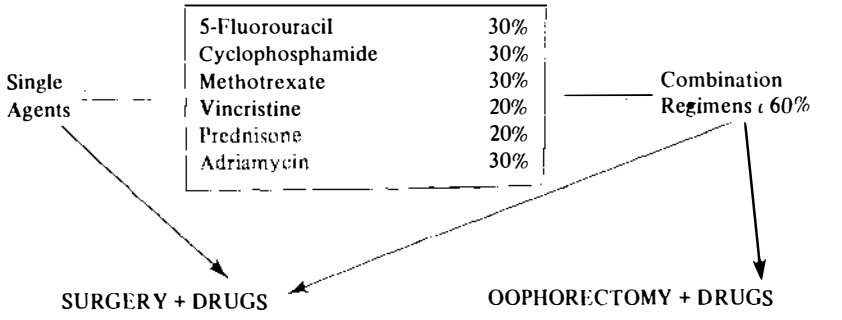

Figure 4 Plan of combined modality therapy in breast cancer. Six different single agents produce 20-30% objective response and combinations of these can yield an approximate 60% response rate.

Treatment and the Breast Cancer Task Force aimed at the use of chemotherapy in the earlier stages of treatment. A specific plan of combined modality therapy in breast cancer is shown in Figure 4.

Of all the major solid tumors, breast cancer is one of the most responsive to chemotherapy. Various agents have the ability to produce a significant number of objective regressions, as shown in the Cancer Therapy Evaluation Program summary of pooled results for single agents given in Table 5. In general, five drugs have been most active: 5-FU, Cytoxan, methotrexate, vincristine, and prednisone (which alone has an overall response rate of ~ 20%).

Table 5 Summary of single agents active against advanced breast cancer

Drug	No. Evaluable Patients	No. Objective Responses	Response (%)
Alkylating agents			
Cyclophosphamide	165	52	31.5
Nitrogen mustard	92	32	35
Phenylalanine mustard	86	20	23
Chlorambucil	54	11	20.4
Thio-TEPA	162	48	30
Antimetabolites			
5-fluorouracil	1052	310	29
Methotrexate	259	87	33.6
6-Mercaptopurine	45	6	13
Arabinosyl cytosine	64	6	9
Vinca Alkaloids			
Vincristine	164	32	19.5
Vinblastine	95	19	20
Antibiotics			
Actinomycin D	44	5	11
Mithramycin	32	5	16
Mitomycin	60	23	38
Miscellaneous agents			
Hydroxyurea	21	4	20
BCNU	40	15	37

The basic tools, therefore, for a combined approach have existed for a long time. Greenspan (192), at Mt. Sinai Hospital in New York, first reported that a combination of methotrexate and thio-TEPA gave a 60% response rate (25 of 40 patients). In 1966 he reported (193) that multiple drug therapy consisting of thio-TEPA, methotrexate, cyclophosphamide, 5-FU, and testosterone produced regressions in 59 of 73 patients (81%).

At the American Association for Cancer Research Meeting in 1969, Dr. Richard Cooper of the Buffalo Medical Group presented a study combining five drugs as follows: 5-fluorouracil: 12 mg/kg/day X 4, then 500 mg/wk iv; methotrexate: 25–50

gm/wk iv; vincristine: 35 μg/kg/wk iv; cyclophosphamide: 2.5 mg/kg/day po; and prednisone: 0.75 mg/kg/day po (194). He reported responses in 90% (54 of 60) of patients treated. This initial report stimulated wide-ranging studies of combination regimens, and data now are available on 323 patients treated with intensive combination chemotherapy. Objective responses have been reported in 244, or more than 75%. Even if the results of Cooper are excluded, the overall response is still 56% and indicates a significant potential for cell kill in a large percentage of patients with advanced breast cancer. Responses to various therapeutic modalities available are compared in Table 6.

Table 6 Comparison of therapeutic modalities in breast cancer

Modality	Response (%)
Oophorectomy	40–50
Hormonal ablative surgery	30–40
Androgens	20
Estrogens	35
Single agent chemotherapy	30
Combination chemotherapy	56–75

Clearly, chemotherapy should be involved in the therapeutic approach at an earlier stage of disease and treatment, perhaps in combination with other therapeutic modalities so as to attempt to use the large cell kill potential when, theoretically at least, the amount of residual disease is smaller. It is hoped this will lead to an increased incidence of disease-free survival.

CONCLUSION

Chemotherapy is still a relatively new modality of cancer therapy, dating back only to 1946 with the initial clinical trials of nitrogen mustard. A wide range of active agents with a broad variety of applications has since developed. As a result, a Subspeciality Board of Medical Oncology has been approved by the American Board of Internal Medicine. The curative potential of chemotherapy alone, or combined with surgery and/or radiotherapy, has been established in at least eight tumors which, unfortunately, account for only a little over 10% of cancers. In five other tumors, chemotherapy is associated with enhanced survival, and it is thought that combined modality approaches offer an immediate chance of even greater survival gains and possible cure. This is especially true for adenocarcinoma of the breast and ovary, two of the major cancers causing death in women.

Palliation for advanced solid tumors is a major role of chemotherapy today, and its value to patients should not be downgraded. It is often forgotten that most of internal medicine practice is palliation of disease after the excitement of making the

differential diagnosis. Still, the ultimate future of chemotherapy for solid tumors does not lie in palliation alone but in combination with surgery and radiotherapy in the treatment of primary disease. The localized modalities of surgery and radiation therapy fail in many cases, not because they do not eradicate the primary disease but because microscopic metastatic foci exist outside the treated area. It is hoped that in palliative treatment for advanced disease, regimens of cytotoxic potential will be uncovered which, when used in the primary therapeutic approach as an adjuvant to surgical therapy or radiotherapy, will destroy metastatic foci and increase the number of patients who survive free of disease indefinitely.

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