Adriamycin—A Review

Cytotoxic chemotherapy as a modality in modern cancer therapy began about 30 years ago with the discovery of the clinical activity of nitrogen mustard by a group at the Sloan-Kettering Memorial Hospital, New York, New York. Since then, the armamentarium of the chemotherapist has grown substantially and is one of the major factors that led to full flowering of medical oncology as a subspeciality of internal medicine. Today, more than 30 cytotoxic drugs are available with a wide range of structures, mechanisms of action, and clinical activity. These antitumor drugs come from a variety of sources (synthetic chemicals, antibiotics, plant products, enzymes) obtained in different geographic locations. Adriamycin, a new drug that recently became commercially available in the United States, is adding significantly to the effects achieved with cancer chemotherapy. It is the purpose of this editorial to put this drug into current perspective.

PRECLINICAL STUDIES

Adriamycin is an anthracycline antibiotic originally isolated by aerobic fermentation of Streptomyces peucetius caesius and by solvent extraction of chromatographic purification (1). Structurally, adriamycin is an analogue of daunorubicin, an earlier clinical compound, differing from it only in the hydroxylation of the 14th carbon (text-fig. 1). Daunorubicin has clinical activity against acute leukemia, but a narrow therapeutic index (TI) limits its usefulness. The biologic activity of adriamycin is related to its ability to bind specifically with DNA by intercalation between adjacent base pairs of the double helical structure (2, 3). This property, inducing stereochemical template disordering, inhibits the enzymes involved in DNA replication (DNA-dependent DNA polymerase) and transcription (DNA-dependent RNA polymerase) (4). These results, obtained by studies of cell-free systems, are consistent with the biologic data obtained in in vivo and cell cultures (i.e., inhibition of the incorporation of precursors into DNA and RNA, inhibition of mitosis, and induction of chromosome aberrations (5–8)).

Adriamycin was developed by the Farmitalia Company, Milan, Italy, and its choice over daunorubicin was based on data from the Ehrlich ascites tumor in mice (9, 10). Activity has also been observed in C57BL mice with transplanted lymphosarcoma (9), rats bearing Oberling-Guérin-Guérin myeloma (10), mice bearing sarcoma 180 (9), and in leukemia L1210 (11), the major screening tool in the drug development program of the Division of Cancer Treatment (DCT). Activity in other systems was also described (12–14).

At the cell level, the drug has an immediate and dose-related inhibitory effect on mitosis (5). At low doses, the inhibition is at the preprophase stage, whereas at higher doses the mitotic block is complete. Adriamycin induces chromosome aberration in human leukocyte cultures (15). The extent and type of chromosome aberration is dose related, with increasing frequency and severity as the drug dose is increased. The changes observed have been mutagenic (8).

Adriamycin also has immunosuppressive effects. It significantly inhibits the titer of hemolytic and hemagglutinating antibodies in mice immunized with sheep red blood cells. The greatest immunodepressant effect was recorded when adriamycin was administered after antigen administration, thus indicating that adriamycin does not act on the very early steps of the immune response (16, 17). Activity has also been observed in both the primary and transplanted tumors induced by the Moloney strain of murine sarcoma virus in mice (18) and female DBA/2 mice bearing ascites lymphocytic leukemia P-288 (19).

Pharmacologic studies show that adriamycin administered iv is rapidly cleared from the plasma of rodents, with concentration of the drug in the liver, spleen, kidney, lung, and heart (20, 21). Drug excretion is prolonged and occurs predominantly via the liver.


Editor's note: Periodically, the Journal publishes solicited guest editorials as a means of transmitting to investigators in cancer research the essence of current work in a special field of study. The Board of Editors welcomes suggestions for future editorials that succinctly summarize current work toward a clearly defined hypothesis regarding the causes or cure of cancer.
The pharmacology of adriamycin in man has been extensively studied by Benjamin et al. (22-24), Bachur et al. (25), and DiFronzo et al. (26). The drug has a rapid plasma clearance and a large volume of distribution, suggesting wide dispersion into the tissue (22, 26). There is minimal urinary excretion, with only 5% of the drug excreted during the first 5 days, as measured by fluorimetric methods; this suggests extensive tissue binding. After injection of a tritium-labeled drug at a dose of 0.5 mg/kg, 50% of the radioactivity was detected in the feces in 7 days, whereas in patients with impaired hepatic function, the radioactivity dropped to only 20% (26).

Adriamycin is metabolized predominantly by the liver to adriamycanol and several aglycone derivatives; approximately half the drug is excreted intact in the bile, with an additional 30% excreted as conjugates (22, 25). Pharmacokinetic studies in patients with hepatic dysfunction show significant, prolonged plasma levels of adriamycin; metabolites are associated with exaggerated clinical toxicity (24). These observations are the basis of a requirement for dose deescalation in patients with impaired hepatic function.

**CLINICAL STUDIES**

Adriamycin has been clinically tested in the United States since 1969, and over 3,000 patients have been treated with the drug alone or in combination with other chemotherapeutic agents.

One of the most impressive aspects of the antitumor effect of adriamycin is its broad spectrum of activity (table 1). In nine tumor categories adriamycin has established antitumor activity. These encompass a broad range of solid tumors that in the past have been relatively insensitive to chemotherapy, especially the soft tissue and bone sarcomas and bladder cancer.

In seven additional tumor categories available data indicate some degree of adriamycin activity, although a definitive statement cannot be made yet. This group also includes some classically unresponsive tumor types such as cancer of the stomach and prostate. Only three tumor categories are unresponsive to adriamycin; they include some tumors that generally are least sensitive to chemotherapy (e.g., renal cancer and malignant melanoma). Despite the extensive clinical testing of adriamycin, there are still five categories for which no adequate data exist. This will soon be rectified, since various cooperative clinical groups have nearly all these tumors under phase II evaluation with adriamycin.

When an experimental drug is active in phase II evaluations, a study approach is established involving both clinical trials and preclinical laboratories (text-fig. 2). In clinical studies, the new drug is combined with other active drugs or integrated into established combinations to increase the therapeutic activity against advanced disease. Additionally, in keeping with the overall thrust of combined modality attacks against cancer (27), a new active drug is combined with surgery and/or radiotherapy and/or immunotherapy to increase the remission rate for primary therapy. The current status of the flow of adriamycin into combination regimens and combined-modality approaches is outlined in table 2. Simultaneously, the following ranges of approaches are taken to improve the T1 of an active drug: 1) schedule manipulation, 2) dose manipulation, 3) pharmacologic investigations, 4) attempts to block toxicity, and 5) clinical experience. Finally, a vigorous search for analogues is made to find a new drug with greater efficacy and/or diminished toxicity.

Adriamycin has been used on a wide range of dose schedules. The following are the initial adriamycin dose schedules for all phase IV.

<table>
<thead>
<tr>
<th>Drug Activity Established</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combination with other drugs</strong></td>
</tr>
<tr>
<td><strong>Combination with other modalities</strong></td>
</tr>
<tr>
<td><strong>Attempt to improve T1</strong></td>
</tr>
<tr>
<td><strong>Search for analogues</strong></td>
</tr>
</tbody>
</table>

**Table 2.--Current status of adriamycin studies**

<table>
<thead>
<tr>
<th>Tumors</th>
<th>Combination regimen superior to single agent</th>
<th>Combined modality role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Yes*</td>
<td>Under test</td>
</tr>
<tr>
<td>Sarcomas:</td>
<td>Excluding osteogenic</td>
<td>Yes*</td>
</tr>
<tr>
<td>Osteogenic</td>
<td>Under test</td>
<td>Positive</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Malignant lymphomas</td>
<td>Yes (various drugs)</td>
<td>Under test</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Testicular cancer</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pediatric tumors</td>
<td>Under test</td>
<td>Under test</td>
</tr>
<tr>
<td>Acute leukemias</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* Single-agent activity studies are being conducted for all tumors listed.
* Adriamycin + cyclophosphamide; adriamycin + cyclophosphamide + 5-FU.
* Adriamycin + DTIC; adriamycin + DTIC + cyclophosphamide + vincristine.

**Table 1.--Antitumor activity spectrum of adriamycin**

<table>
<thead>
<tr>
<th>Established activity</th>
<th>Possible activity</th>
<th>Unresponsive</th>
<th>Data inadequate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast adenocarcinoma</td>
<td>Stomach adenocarcinoma</td>
<td>Large bowel adenocarcinoma</td>
<td>Pancreatic adenocarcinoma</td>
</tr>
<tr>
<td>Soft tissue and bone sarcomas</td>
<td>Ovarian adenocarcinoma</td>
<td>Malignant melanoma</td>
<td>Squamous cell carcinoma of esophagus</td>
</tr>
<tr>
<td>Bladder adenocarcinoma</td>
<td>Prostate adenocarcinoma</td>
<td>Renal cancer</td>
<td>Endometrial adenocarcinoma</td>
</tr>
<tr>
<td>Bronchogenic carcinoma</td>
<td>Squamous cell carcinoma of cervix</td>
<td></td>
<td>Brain tumors</td>
</tr>
<tr>
<td>Testicular carcinoma</td>
<td>Squamous cell carcinoma (head and neck)</td>
<td></td>
<td>Chronic leukemias</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>Hepatoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric solid tumors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant lymphomas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute leukemias</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Rhabdomyosarcomas, which are relatively sensitive to chemotherapy agents, are removed from consideration, this response rate was only 18% (32/179). There were few long-term remissions.

Adriamycin has been active against sarcomas in both adults and children (24, 30, 31, 42-44). The overall response rate is 25% (69/279) for sarcomas of all types and is roughly equivalent for soft tissue sarcomas (27/103 = 26%) and bone and joint sarcomas (23/76 = 30%).

Gottlieb et al. (45) studied adriamycin in combination with 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (DTIC, DIC), another experimental drug having slight activity against sarcomas (46). The drugs in this combination are synergistic in L1210 and P388 murine tumor model systems (47). Clinically, both drugs can be given in combined doses nearly equivalent to those used for each as a single agent. Of 200 sarcoma patients currently evaluable, 85 (43%) achieved an objective response. Although there are some minor differences in response rates by cell type, the number of cases per cell type is not sufficient to demonstrate significant differences.

The addition of vincristine to this combination did not improve the induction rate (42% in 107 patients), but may have increased survival (48). Recently, Gottlieb et al. (48) added Cytoxan to the regimen (now called CY-VA-DIC), which is given iv in courses every 21 days as follows: Adriamycin, 50 mg/m², day 1; Cytoxan, 500 mg/m², day 1; DIC, 250 mg/m², days 1-5; and vincristine, 1 mg/m², days 1-5.

To date, 82 patients are evaluable; there have been 14 complete and 35 partial responses for a 60% overall response rate. The median duration of response will be greater than 6 months, with 43/49 patients (88%) still in remission. The dose-limiting toxicity has been transient leukopenia in one-third of the patients, but serious infections have been rare. This combination regimen appears to represent a significant advance in the therapy of those with metastatic sarcoma.

Currently, a wide range of combinations with adriamycin is being investigated, and only time will tell which combination, if any, will be superior to the two-drug combination of adriamycin plus DTIC.

The chemotherapy of advanced osteosarcoma has improved considerably with the administration of adriamycin alone or in combination with other agents. Cortes et al. (44) at the Roswell Park Memorial Institute demonstrated a significant response rate of 41% (7/17) for adriamycin alone in metastatic osteosarcoma. Rosen et al. (49) reported objective regression in 54% (7/13) of patients with metastatic osteosarcomas treated with a combination of adriamycin and high doses of methotrexate followed by rescue with citrovorum factor.

In the hope of increasing cure rates for osteosarcoma, adriamycin is being studied as a surgical adjuvant. Mortality in osteosarcoma results from metastases in 80-95% of patients with X-ray evidence of pulmonary metastases occurring in a median of 9 months from initial diagnosis (50).

The Acute Leukemia Group B (Scarsdale, N.Y.) has given adriamycin to 21 patients with osteosarcoma within 2 weeks after amputation of the primary lesion. Of the 21 patients, 19 were alive 1+ to 32 months (median, 9+ mo) at the time of the last full report (51). Five of the 21 had relapsed, 2 with local and 3 with pulmonary metastases. By life-table analysis, 71% would be expected to be free of pulmonary metastases in contrast to 30% in a large historic control series. The data dem-
In urinary bladder carcinoma, chemotherapy has been neglected. Adriamycin has been evaluated in 62 patients, with an overall response rate of 35% (21/62) (30, 34, 43, 62); this significant activity is being further examined in several studies.

In thyroid cancer, adriamycin has been studied more extensively than any other antineoplastic agent. Thus far, there is a 30% response rate (14/46) in patients with advanced refractory, metastatic thyroid carcinoma, but analysis in different cell types is not available (29, 34, 35, 63, 64).

Forty-six patients with neuroblastoma have been treated with adriamycin and 15 (33%) have shown objective responses (29, 34, 35, 43, 58, 62, 65). Although this activity is less than that reported (66-68) for cyclophosphamide and vincristine (singly or in combination), the cases treated with adriamycin were unresponsive to prior therapy. Using a combination of adriamycin, cyclophosphamide, vincristine, and methotrexate, Bonadonna et al. (34) reported 4 responses in 9 patients; other combination studies are in progress.

Wilms' tumor is another pediatric solid neoplasm in which activity has been observed (7/17 = 41%) (30, 34, 42, 43, 58).

In 173 refractory cases of acute lymphocytic leukemia, adriamycin has been administered; 44 (25%) had complete remission (21, 34, 35, 43, 58, 69-71). Acute lymphocytic leukemia in children is very responsive to chemotherapy; daunorubicin (the earlier analogue of adriamycin) is the standard anthracycline antibiotic in most combination regimens used in the United States.

Daunorubicin alone produces complete remissions in nearly 50% of previously untreated patients with acute myelocytic leukemia (72). Combination chemotherapy in regimens such as cytosine arabinoside and thioguanine (73) or cytosine arabinoside and daunorubicin (74), which induce a complete remission rate greater than 50%, is the current accepted therapy. With adriamycin, the complete remission rate is 26% (27/102) (24, 34, 42, 43, 62, 69-71, 75, 76). Most of these patients had advanced disease and had received prior chemotherapy. McCredie et al. (77) (M. D. Anderson Hospital and Tumor Institute) induced a complete remission rate of 85% (28/37) in adult leukemia with a combination of adriamycin, vincristine, prednisone, and cytosine arabinoside (Ad-OAP). Further studies are in progress, but daunorubicin is still used in most cooperative studies.

Although adriamycin can shrink masses of bronchogenic carcinoma, it shares the problem of all chemotherapeutic agents in this disease—symptomatic improvement and objective tumor regression have a minimal influence on survival (78). When objective tumor regression greater than 50% was evaluated from 11 series in the literature, the overall response rate was 19% (49/264), with a range of 0-50% (24, 28, 30, 35, 42, 43, 79-81). The effectiveness of adriamycin in relation to other single agents can be evaluated by objective response, but the data on adriamycin are insufficient to judge survival as a response variable. Within the limitation of historic comparisons in which data on performance status and prior chemotherapy and radiotherapy are not always reported and results include regressions less than 50%, adriamycin ranks among the most effective single drugs in the data for over 5,000 cases reported by Selawry and Hansen (79).

Adriamycin is being evaluated in a variety of combinations to increase the response rates in bronchogenic carcinoma.
cancer. The Veterans Administration Lung Cancer Study Group is evaluating adriamycin plus cyclophosphamide, whereas the Central Oncology Group is piloting a study of adriamycin plus 1,3-cis(2-chloroethyl)-1-nitrosourea (CCNU) and hexamethylmelamine. AT M. D. Anderson Hospital, an intensive five-drug combination [bleomycin, adriamycin, CCNU, Oncovin, and nitrogen mustard (BACON)] has been developed by Livingston et al. (82). This regimen was given to 31 patients with advanced cancer, including 11 with lung cancer. Tumor regressions greater than 50% have been observed in 8 of these cases, including one complete response.

At this time, no combination has been established as clearly superior to single agents.

**TOXICITY**

The toxic effects of adriamycin are dose related, predictable, and reversible. The major toxicities are dose-limiting myelosuppression in approximately 60–80% of patients, stomatitis in as many as 80%, nausea and/or vomiting in 20–55%, and alopecia in virtually all cases.

Leukopenia is the predominant hematologic toxicity, and the severity depends on the adriamycin dose and the regenerative capacity of the bone marrow. Thrombocytopenia and anemia occur in the same time frame as leukopenia, but they are not as great a problem. Supportive care for hematologic problems should be available for patients being treated with adriamycin.

Drug-induced stomatitis typically begins as a burning sensation with erythema of the oral mucosa and in 2–3 days may produce frank ulceration, particularly in the sublingual and lateral tongue margins. Retrospective comparison of the incidence of stomatitis as a function of dose schedule suggests that it may be less frequent as the interval increases between doses.

Alopecia involving the scalp, axillary, and pubic hair occurs in almost all patients. Growth of hair usually resumes on cessation of the drug.

Gastrointestinal toxicities evidenced by nausea and occasional vomiting are associated with the drug but rarely limit clinical use. Extravasation during iv administration can produce local tissue necrosis, but normal precautions can prevent this toxicity.

Cardiac toxicity is the unique harmful effect of adriamycin that causes the greatest problem in long-term administration. This toxicity may involve transient electrocardiogram (ECG) abnormalities, definitive cardiomyopathy, or both.

ECG changes associated with adriamycin therapy are reported in 2–30% of the treated patients. These transient abnormalities include supraventricular tachycardias, atrial and ventricular extrasystoles, and ST-T wave changes. The changes usually are transient and occur most frequently in the first few days after drug infusion. Reduction in the R-wave voltage may occur and is usually irreversible; in the series by Cortes et al. (83), it was seen in all patients before adriamycin-induced congestive heart failure developed. The transient ECG changes apparently are not of clinical significance, since no significant morbidity or mortality has been reported.

In contrast to the transient changes, the chronic toxicity of drug-induced cardiomyopathy produces both morbidity and mortality to a significant degree. This “pump” failure is dose dependent, but shows no apparent relationship to preexisting heart disease. The clinical presentation and pathophysiology of cardiac damage by adriamycin are indistinguishable from other known cardiomyopathies. Although the speed of the clinical course varies, it is usually a rapidly progressing syndrome of congestive heart failure and cardiorespiratory decompensation including dilation of the heart, pleural effusion, and venous congestion. Reversibility of the heart failure does not appear to be a function of the therapeutic intervention. In fact, Gilladoga et al. (84) reported that adriamycin cardiomyopathy may be reversed by conventional medical management.

The pathologic findings are limited to changes visible by electron microscopy. The most dramatic change is a marked decrease in the myocardial fibrils accompanied by mitochondrial changes characterized by swelling, focal membrane thickening, and dense inclusions. Other observations include nuclear degeneration, disorganization of the sarcoplasmic reticulum, and depletion of glycogen granules (85). These changes are nonspecific and have been described in other types of cardiomyopathy (86).

The overall incidence of congestive heart failure caused by drug-induced cardiomyopathy is 1%, although this is deceptive since the toxicity is related to the total dose administered. If the total dose is kept below 450 mg/m², cardiomyopathy is not observed (table 3). Unfortunately, this limits the amount and duration of drug therapy. The frequency of cardiomyopathy is markedly increased at total doses above 550 mg/m², so that a clinician who exceeds these dose levels must be aware of the high risk and balance it against the risk of discontinuing therapy in rapidly developing malignancy.

**Table 3. Frequency of cardiomyopathy in relation to total adriamycin dose in adults**

<table>
<thead>
<tr>
<th>Adriamycin total dose (mg/m²)</th>
<th>Number of patients at risk</th>
<th>Number of patients with cardiomyopathy</th>
<th>Frequency (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;450</td>
<td>668</td>
<td>0</td>
<td>0</td>
<td>(85)</td>
</tr>
<tr>
<td>&gt;450</td>
<td>100</td>
<td>75</td>
<td>0</td>
<td>(83)</td>
</tr>
<tr>
<td>&gt;500</td>
<td>410</td>
<td>22</td>
<td>0</td>
<td>(83)</td>
</tr>
<tr>
<td>&gt;550</td>
<td>510</td>
<td>31</td>
<td>0</td>
<td>(83)</td>
</tr>
<tr>
<td>&gt;600</td>
<td>663</td>
<td>14</td>
<td>1</td>
<td>(83)</td>
</tr>
<tr>
<td>&gt;700</td>
<td>800</td>
<td>14</td>
<td>1</td>
<td>(83)</td>
</tr>
<tr>
<td>&gt;800</td>
<td>100</td>
<td>27</td>
<td>7</td>
<td>(83)</td>
</tr>
<tr>
<td>&gt;900</td>
<td>1000</td>
<td>10</td>
<td>3</td>
<td>(83)</td>
</tr>
<tr>
<td>&gt;1000</td>
<td></td>
<td>10</td>
<td>2</td>
<td>(83)</td>
</tr>
</tbody>
</table>

Rinehart et al. (87), who used a prejection period to left ventricular ejection time ratios (PEP/LVET) to estimate left ventricular function, reported that 7 of 8 adult patients receiving adriamycin (300–525 mg/m²) had a significant increase in the PEP/LVET ratio. In contrast, only 1 of 8 patients receiving less than 200 mg/m² developed prolongation of the PEP/LVET ratio. It appears that the systolic time interval may be a sensitive noninvasive indicator in predicting cardiotoxicity, although this requires confirmation.

Jones et al. (88) have data supporting echocardiography as useful for the detection of adriamycin-induced heart disease. They performed an ECG analysis (with calculation of the ejection fraction) on 51 cancer patients being treated with adriamycin. Only 1 of 48 (2%) who received less than 400 mg adriamycin/m² had an ejection fraction of less than 0.48, whereas 6 of 13 (46%) who received more than this dose had an ejection fraction of less than 0.43 (P<0.001). Only 2 of these patients had clinical findings of congestive heart failure; this indicates a subclinical damage due to adriamycin.
that can be picked up through echocardiographic analysis.

ADRIAMYCIN ANALOGUES

As soon as the dramatic activity of adriamycin was elucidated, a vigorous search for analogues began by the drug research and development program of the DCT. This has involved a wide range of compounds developed in Western Europe and the Soviet Union. Twelve of these compounds, including 6 that have undergone some degree of clinical trial abroad, have been evaluated by the Laboratory of Experimental Chemotherapy at DCT (table 4).

Table 4.—Daunomycin and adriamycin analogues under evaluation in comparison to parent compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinerubin A (NSC-18334)</td>
<td>Ciba Pharmaceutical Products Inc., Summit, N.J.</td>
</tr>
<tr>
<td>Cinerubin B (NSC-18335)</td>
<td>Ciba Pharmaceutical Products Inc., Summit, N.J.</td>
</tr>
<tr>
<td>Rubidazone (NSC-164011)</td>
<td>Rhone-Poulenc, France</td>
</tr>
<tr>
<td>Daunomycin-DNA complex (NSC-169531)</td>
<td>Belgium</td>
</tr>
<tr>
<td>Carminomycin (NSC-180024)</td>
<td>U.S.S.R.</td>
</tr>
<tr>
<td>Dubromycin (NSC-180510)</td>
<td>Rhone-Poulenc, France</td>
</tr>
<tr>
<td>Daunomycin-13-formylhydrazone (NSC-180511)</td>
<td>Rhone-Poulenc, France</td>
</tr>
</tbody>
</table>

* Have had some degree of clinical trial abroad.

Among the analogues with the most clinical data available is rubidazone, a benzoylhydrazide derivative of daunorubicin. The activity of rubidazone in experimental tumor systems is superior to daunorubicin but not more effective than adriamycin (Goldin A: Personal communication). Rubidazone is less toxic than adriamycin and similar to daunorubicin in cardiac toxicity studies in the hamster. In other in vitro and in vivo animal tests, rubidazone is less toxic than either daunorubicin or adriamycin (89). Studies in the rabbit cardiac toxicity model (90) indicate that rubidazone does cause cardiac toxicity but at a higher total dose than adriamycin (Young D: Personal communication). This could be deceptive in the prediction of toxicity for man, since much higher doses are used in a single course of rubidazone treatment when compared with adriamycin (91-97). A phase I clinical trial in the United States is just ready to begin at M. D. Anderson Hospital.

Both dubromycin and daunomycin-13-formylhydrazone have received some clinical evaluation in France, but are clinically less impressive than rubidazone (Jacquillat C: Personal communication).

Carminomycin is an analogue of daunorubicin originally isolated from the mycelium of Actinomadura carminata by Brazhnikova et al. (94) at the Institute of New Antibiotics, Academy of Medical Sciences, Moscow, U.S.S.R. The structure has been described in (95). Experimental studies in the United States show that carminomycin has significant antitumor activity but lacks superiority to adriamycin in all systems studied (Goldin A: Personal communication). Clinical trials in progress in the U.S.S.R. show an acute toxicity spectrum not dissimilar to other drugs in this class (Perevodilohova N: Personal communication).

The complexing of adriamycin or daunorubicin with DNA is based on the hypothesis of Trouet et al. (96) and DeDuve and Trouet (97): they post that DNA confers lysosomotropic properties on the drugs and enables them to achieve selectively higher incorporation into the neoplastic cells. Experimental tumor studies in Belgium and at the NCI have indicated potentially less toxicity and increased efficacy for the DNA complexes. The experimental picture has been complicated by an NCI formulation of adriamycin-DNA showing less activity than the original formulations of Trouet and his associates, and the NCI is attempting to prepare a new formulation. Clinical studies with both complexes have been undertaken in Europe, but their preliminary nature precludes any judgment at this time. Clearly, additional work should be vigorously pursued on this approach.

The most critical questions in analogue searching after a drug is shown to be active are: a) What is the basis for choosing a new analogue for clinical evaluation? and b) how should its clinical trial be approached? These basic approaches are being considered for adriamycin analogues:

I. Experimental tumor data
   A. Superiority over adriamycin
   B. Activity in a system unresponsive to adriamycin

II. Toxicology data
   A. Lack of cardiac toxicity
   B. Lack of marrow toxicity

III. Clinical experience in other countries
   A. Clinical activity
   B. Toxicity

Experimental tumor data are most commonly used in choosing a new analogue in most drug development programs. The same experimental tumor systems used to predict activity of the parent compound can be employed to find superior activity for an analogue. This is most easily accomplished when the parent compound is only weakly or moderately active, as is the case with adriamycin in the leukemia L1210 system. It becomes more difficult when the parent compound is already curative to a high degree in a system such as adriamycin in B16 melanoma and P388 leukemia. A second experimental design would be the screening for activity in systems completely unresponsive to adriamycin. This approach is taken in many analogue drug development programs, which use tumor panels to search for differential tumor spectra (98).

A toxicologic model could also be incorporated in the decision-making process for choosing an adriamycin analogue for clinical trial. Since dose-related cardiac toxicity is the major limitation to protracted use of adriamycin, a drug with diminished potential for cardiac toxicity, even with less efficacy, would be highly desirable. Potential models in the rabbit, monkey, hamster, and rat have been postulated to have some degree of predictive value; all the models will be investigated in further detail.

The third major approach in choosing an analogue is examination of the data base of clinical experience in other countries. As stated earlier, six analogues of adriamycin and daunomycin have been clinically evaluated abroad, and the information on activity and toxicity will obviously have a major function in the decision of which ones might undergo widespread trial in the United States.
ADRIAMYCIN

After an analogue has been selected for clinical trial, the strategy of testing becomes of paramount importance and must be designed from both the standpoint of efficacy and toxicity. The efficacy of the analogue could be compared to Adriamycin in either tumors highly or moderately responsive to Adriamycin or in unresponsive tumors. The major problem with highly responsive tumors is that drug combinations involving Adriamycin have the highest priority within the treatment strategy for these tumors. It would be unrealistic to expect a valid test of an analogue in patients previously treated with Adriamycin in a combination setting. It might be equally unrealistic to pursue a single-agent trial with an unproved analogue when superior combinations exist. The same problems arise to a lesser degree in moderately responsive tumors, and it is not unrealistic to contemplate a single-agent trial with an analogue in previously untreated patients with bronchogenic carcinoma. The tumors unresponsive to Adriamycin are relatively easy to use for analogue testing; used alone, however, they might not constitute a fair trial of the predictive ability in the decision-making process.

When evaluation of the cardiac toxicity of a new analogue is brought into focus, the problems are manifold. A physician could maintain patients who are responsive to an analogue as long as relapse is prevented and observe for congestive heart failure. This occurred with Adriamycin when physicians knew of the toxic potential of daunorubicin. Although “ignorance is bliss” to some extent, a continued approach in this manner might not be defensible. An attempt could be made to use ECG or other noninvasive measurements, but their past value in the prediction of the chronic toxicity has been questionable.

CONCLUSION

Chemotherapy is now a well-established modality. As with other therapeutic measures, chemotherapy can be curative or palliative in varying degrees, depending on the individual tumor. “Cure” means that the life expectancy of treated cancer patients is the same as “normal” life expectancy—specifically, the same as that of a matched cohort in the general population. Cures or at least possible cures from drugs alone have been obtained in such diseases as choriocarcinoma, Burkitt’s lymphoma, acute lymphocytic leukemia, testicular cancer, and Hodgkin’s disease (99). Chemotherapy combined with X-ray and/or surgery promises cures in many patients with childhood solid neoplasms such as Wilms’ tumor, embryonal rhabdomyosarcoma, and Ewing’s sarcoma. In other tumors, chemotherapy achieves a significant degree of cell kill, which is reflected in a high rate of objective tumor regression and enhanced survival, although cure cannot be shown at this time. These tumors include adenocarcinoma of the breast and ovary, non-Hodgkin’s lymphoma, multiple myeloma, the chronic leukemias, and acute granulocytic leukemia. In many of the remaining diseases, chemotherapy can achieve objective regression of disease with palliative benefit to one-fifth to one-third of the patients treated.

A major approach to improving the cure rates in cancer treatment involves the integration of chemotherapy with the local modalities of surgery and radiotherapy applied against solid tumors. Such an approach has been elucidated by the DCT (27). The philosophic base of this combined modality approach is the recognition that surgery and radiotherapy are local modalities that kill tumor cells only where the modalities are applied. They fail to cure many patients, even when they remove all the tumor visible to the naked eye or on diagnostic X-ray film. This failure is thought to be due to dissemination, microscopic disease foci present at the time of surgical excision of the primary tumor that often includes the surrounding tissue and part of the regional lymph nodes.

Chemotherapy, used optimally, has the potential for eradicating the metastatic foci of early disease. In the DCT strategy, the drug regimens showing the highest degree of activity in advanced disease will be the prime candidates for the combined modality approach. The degree of cell kill necessary to shrink a bulky, solid tumor mass by greater than 50% (usually the minimum definition of objective regression) is quite large. If this level of cell kill could be directed against the relatively small tumor burden remaining after surgical excision, perhaps the last neoplastic cell can be eradicated.

Experimentally, it is well established that the best chance of eradicating a tumor mass with chemotherapy is when the tumor cell population is small, a situation occurring immediately after resection of the primary tumor. The ability of chemotherapy to produce a cure is greater when all visible tumor is surgically excised than after subtotal resection (100–102). The inverse relation between tumor cell population and chance of eradicating a tumor mass with chemotherapy is quite large.

The DCT proposed therapeutic strategy for increasing cure rates in solid tumors involves integration of drugs into combined modalities for primary treatment according to the following sequential approach: Test new drugs and combinations in advanced disease; develop an optimum chemotherapy regimen for primary treatment of disseminated disease; and integrate the optimum chemotherapy regimen into a combined modality approach for primary treatment of local and regional disease. In this scheme, new drugs and drug combinations would be tested in advanced disease, and those showing positive results would move into primary treatment of disseminated disease. The optimal regimen evolved in this situation would then be integrated into a combined modality approach for primary treatment of local and regional disease.

Adriamycin is a major addition to the armamentarium available to the oncologist in this strategic approach. In breast cancer (the sarcomas and lymphomas), combined modality trials with the use of Adriamycin in early disease are either under way or planned, and the continued study in advanced disease is of a high order. The DCT is giving high priority to studies of the mechanism of action and pharmacology of the anthracycline antibiotics to improve the TI and uncover superior analogues.

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