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The Clinical Evaluation of Analogs – III. Anthracyclines

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Adriamycin is one of the few examples in the short history of cancer chemotherapy of an analog that is superior to its parent compound [2, 4]. The parent compound in this case was daunomycin (daunorubicin), which had been shown to be active in acute leukemia but had also been shown to have a slim therapeutic index with severe hematologic toxicity that precluded its successful use against the more common solid tumors. Adriamycin has been shown to have a broader spectrum of activity and a superior therapeutic index than daunomycin.

In the original clinical studies, daunomycin maintenance therapy had been shown to be associated with a fatal cardiomyopathy, which appeared to be dose-related as it occurred after the total doses administered exceeded 20–30 mg/kg. As adriamycin's clinical activity was observed, many responding patients were placed on maintenance treatment and again dose-related cardiomyopathy occurred, which limited the duration of successful maintenance that could be adminiistered. Because the range of adriamycin's clinical activities was so much wider than that of daunomycin, the discussions of dose-limiting cardiomyopathy with adriamycin caused a flurry of investigation into the mechanism of the cardiac damage and into ways to predict it, evaluate it, and ameliorate it. Analog development work increased in many countries. Therefore, analogs have entered clinical trial from sources as varied as the Soviet Union (carminomycin), Japan (aclacinomycin), Spain (quelamycin), the United States (AD-32), Italy (4′ epi-adriamycin), and France (rubidazone and 14 DEA daunorubicin). Only some of these drugs have shown either significant superiority of antitumor activity in experimental tumors or diminished cardiac toxicity in animal model systems compared with adriamycin.

Adriamycin has been tested clinically in the United States since 1969, and a massive number of 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 14 tumor categories adriamycin has established anticancer activ-

Table 1. Antitumor activity spectrum of adriamycin

Established activity	Possible activity	Unresponsive
Breast adenocarcinoma	Squamous-cell carcinoma of cervix	Large-bowel adenocarcinoma
Soft-tissue and bone sarcomas	Squamous-cell carcinoma (head and neck)	Malignant melanoma
Bladder adenocarcinoma	Multiple myeloma	Renal cancer
Bronchogenic carcinoma	Pancreatic adenocarcinoma	Malignant gliomas
Testicular carcinoma		Squamous-cell carcinoma of the esophagus
Prostatic adenocarcinoma		
Thyroid carcinoma		
Pediatric solid tumors		
Malignant lymphomas		
Acute leukemias		
Stomach adenocarcinoma		
Hepatoma		
Ovarian adenocarcinoma		
Endometrial carcinoma		

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ity. 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 four additional tumor categories the data available indicate some degree of adriamycin activity, although a definitive statement cannot be made yet. This group also includes some classically unresponsive tumor types.

The toxic effects of adriamycin are dose-related, predictable, and for the most part 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 manifestation of toxicity, and the severity depends on the adriamycin dose and the regenerative capacity of the bone marrow.

Drug-induced stomatitis typically begins as a burning sensation with erythema of the oral mucosa, and in 2—3 days it may produce frank ulceration, particularly in the sublingual and lateral tongue margins. Alopecia involving the scalp, axillary, and pubic hair occurs in almost all patients. Growth of hair usually resumes on cessation of the drug. Gastrointestinal toxicity evidenced by nausea and occasional vomiting is associated with the drug, but rarely limits clinical use. Extravasation during IV administration can produce local tissue necrosis, but normal precautions can prevent this toxic effect.

Cardiac toxicity is the one 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. The chronic toxicity of drug-induced cardiomyopathy produces both morbidity and mortality to a significant degree [7—9]. This 'pump' failure is dose-dependent, but shows no apparent relationship to pre-existing 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 invention.

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/m^2, cardiomyopathy is rarely observed. Unfortunately, this limits the amount and duration of drug therapy. The frequency of cardiomyopathy is markedly increased at total doses above 550 mg/m^2, 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.

Von Hoff [10] has analyzed 4,018 patients treated with adriamycin in the United States cooperative groups between March 1970 and March 1977. A range of variables were recorded for all patients. These totalled 67 and included age, sex, race, performance status, tumor type, prior cardiac disease, prior anticancer treatment, and concomitant treatment with other drugs. Ten specific parameters were looked at in relation to the development of congestive heart failure (CHF) caused by adriamycin. These consisted of total dose and schedule of drug administration, concomitant chemotherapy, prior radiotherapy to the mediastinum, prior cardiac disease, age, sex, race, type of tumor, and performance status.

In this analysis, adriamycin-induced CHF occurred in 88 cases (2.2%). This was observed at intervals ranging from 0 to 231 days, with a median of 23 days, after the last administration of the drug. The mean and median total dosages of the anthracycline received by the patient with CHF were 364 and 390 mg/m^2, respectively. Death occurred within 70 days after the diagnosis of CHF in 63 of the 88 patients. In only 38 of the 63 was death attributed to the CHF. In the others it was attributed to progressive disease. In these latter 25 cases, the CHF was stable but unresolved in 12, partially resolved in 8, and totally resolved in 5.

In this analysis, the total dose of adriamycin was related strongly to the development of CHF. The cumulative probability of developing drug-induced CHF was 0.3 at 400 mg/m^2, 0.7 at 550 mg/m^2, and 0.18 at 700 mg/m^2. When the schedule was examined, the weekly schedule had the lowest incidence of CHF at 0.8% (8/967), the incidence with a single dose every 3 weeks was 2.9% (66/2262), and the three consecutive daily doses repeated every 3 weeks involved an incidence of 2.5% (14/576).

The importance of adriamycin as a clinically useful compound has led to a variety of approaches to improving the therapeutic index by diminishing the cardiac toxicity. These have included: (1) the search for new analogs; (2) schedule manipulation; (3) the use of cardiac toxicity blocking agents.

A major strategic difficulty in clinical evaluation of any of these approaches is defining a feasible and appropriate end-point for protocol studies. The discovery that adriamycin caused cardiomyopathy was empirical. As responding patients were maintained on the drug, the clinical picture was observed. Retrospective analysis determined that it was a dose-related phenomenon. The utilization of clinically manifest cardiomyopathy as a prospective end point is fraught with ethical and logistic

difficulties. Unfortunately no noninvasive diagnostic techniques reliable enough to be utilized in this manner have yet been discovered. The endomyocardial biopsy technique, initially described by Daniels et al. [1, 3] at Stanford, currently offers the only reliable test for prospective use. The cardiac biopsy data previously reported indicate that the pathologic insult to the heart is nearly universal when total doses in excess of 200–250 mg/m^2 are administered. This pathologic insult can be reproducibly graded after electron microscopy evaluation. It offers the possibility of measuring the cardiac damage occurring with an analog, new schedule, or blocking agent at a time when the pathologic insult is subclinical. It is therefore an ethically feasible approach.

There are four possible ways in which a new anthracycline analog of adriamycin could show superiority to its parent compound:

1. Increased efficacy in tumors responsive to adriamycin, as measured by (a) increased complete response rate; (b) increased overall response rate (CR + PR); (c) increased duration of remission; (d) increased survival.

2. Efficacy in tumors unresponsive to adriamycin, e.g., adenocarcinoma of the large bowel, malignant melanoma, renal carcinoma.

3. Diminished acute toxicity as measured by (a) decreased leukopenia and/or thrombocytopenia; (b) decreased stomatitis; (c) decreased alopecia: (d) decreased gastrointestinal toxicity.

4. Diminished cardiac (chronic) toxicity as measured by (a) less cardiac functional damage, as measured by noninvasive techniques; (b) less pathologic damage obvious on endomyocardial biopsy; (c) diminished incidence of clinical cardiomyopathy.

The clinical evaluation for a new anthracycline has to be tailored to fit which ever possibility of improving the therapeutic index is of highest priority. An attempt at a rough combination of the varying possibilities in an

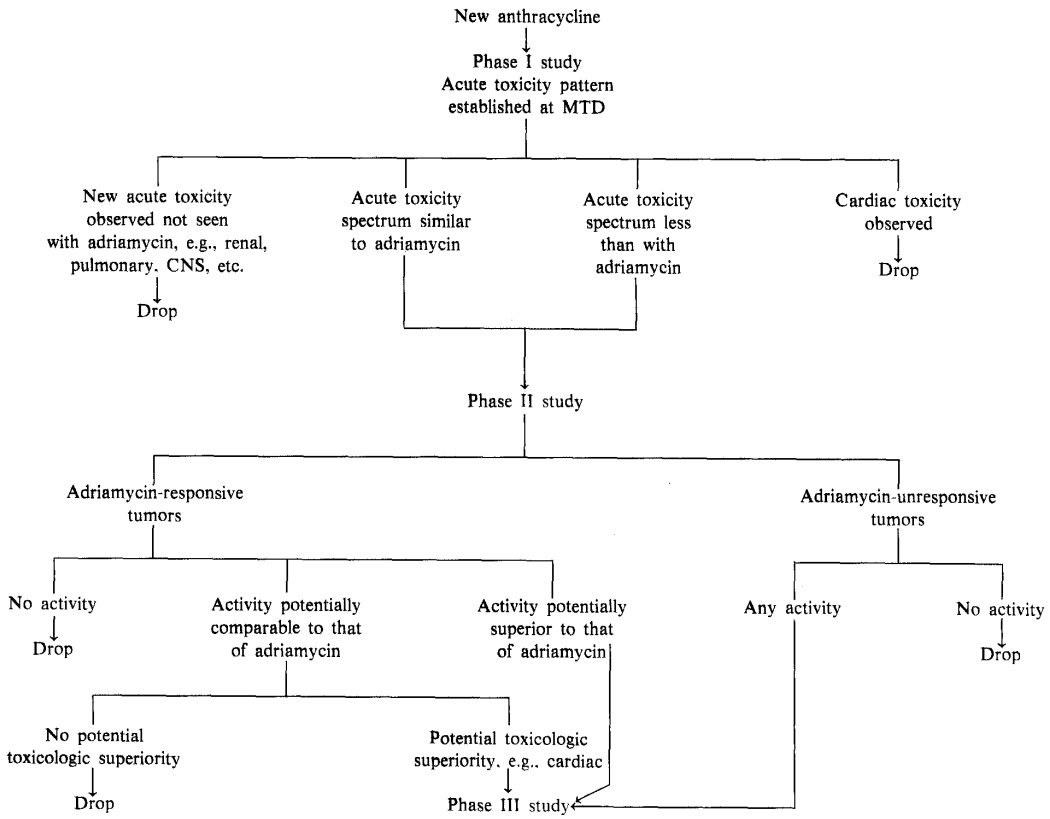

Fig. 1. Hypothetical phase I and II decision flow for new anthracycline

initial schema is shown in Fig. 1. This is just a skeleton, on which the actual criteria would need to be fleshed out in greater detail.

Phase I Evaluation

An appropriate initial schedule should be chosen on the basis of careful evaluation of the preclinical data. Among the preclinical data that should be evaluated are the following:

a) Optimal schedule in the experimental tumors that are responsive to the drug

b) Cell-cycle specificity or the lack of this

c) Toxicology of the drug in rodents and large animals

d) Pharmacology of the drug in experimental animals and correlation with all the above

e) Appropriate biochemical data.

An appropriate starting dose level should be chosen from analysis of the animal toxicology data. The most commonly used approach is to take a third of the toxic dose low (minimally toxic dose) of the most sensitive large animal species, worked out in milligrams per square meter of body surface area. The safety of this approach has been demonstrated in a wide range of drugs, including anthracyclines, by the retrospective analysis of Goldsmith et al. [6].

An appropriate dose escalation procedure should be designed, based on analysis of the preclinical data, including the steepness of the toxicologic dose-response curve. It has been shown by the members of the National Cancer Institute's Phase I working groups that, with all drugs analyzed to date, a completely nontoxic dose can safely be doubled. This will allow a more rapid escalation than could be accomplished with a modified Fibinocci search scheme approach, as originally described by Selawry [10]. Doses should not be escalated in the same patient, so the potential for cumulative toxicity can be evaluated at each dose level, unless this is not considered in the best interests of the patient. Ideally, pharmacologic determinations should be made at each dose level, and if it is deemed appropriate on the basis of the data obtained, the initial schedule can be modified.

The end-points of the study would be as follows:

a) The establishment of a maximally tolerated dose on the schedule tested and a recommended dose level for Phase II evaluation

b) Elucidation of the acute toxicity pattern at all dose levels

c) Elucidation of the pharmakokinetics of the drug in man, so as to make correlations with the pharmacokinetics in animals

d) Early indication of the cardiac toxic potential of the drug

e) Early indication of the therapeutic efficacy of the drug, recognizing that patients who are placed on Phase I study often do not have measurable disease and may be extensively pretreated with other modalities and/or drugs.

With a new anthracycline, there are four possibilities regarding acute toxicity in comparison to adriamycin. One possibility is that the analog will have a similar pattern, i.e., drug-limiting myelosuppression, stomatitis, alopecia, ulceration on extravasation, and mild gastrointestinal side effects. A second possibility is that the analog may have a more favorable pattern, with some of the toxic manifestations less severe than those seen with adriamycin. A third possibility would be the observation of a new qualitative toxicity with the analog. One example of this is the jaw pain and postural hypotension observed with cyclocytidine and not seen with its parent drug arabinosyl cytosine. If a new anthracycline demonstrated renal toxicity, hepatic toxicity, neurologic toxicity, or pulmonary toxicity, this might be a sufficient reason to drop the drug after the phase I study. Any anthracycline that demonstrated acute cardiac toxicity would obviously not be a prime candidate for further evaluation. The fourth possibility is some mixture of all of the above, and then the trade-offs would have to be carefully examined in the decision-making process.

Phase II Evaluation

Phase II evaluation becomes a disease-oriented process, and so with a cancer drug a variety of phase II strategies appropriate to the many diseases which constitute the cancer spectrum needs to be developed. With an analog, the evaluation must always involve a comparison with the known available data on the parent drug in each disease studied. In terms of efficacy, there are three possibilities for an analog that can be tested for in a phase II design. The first is that the analog will be more active against a responsive tumor. The second is that the analog will have activity in a tumor that is unresponsive to the parent drug. The third possibility is that the analog will not be cross-resistant with the parent drug. In this last case, activity with the analog would be demonstrated after progressive disease was seen on the parent drug. Vincristine and vinblastine are examples of close structural analogs that are not cross-resistant. The phase II strategy for a new anthracycline would very much depend on which possibility was being evaluated. If increased efficacy were being sought, then a clinical situation would have to be developed where the analog would be given as a single agent without prior exposure

to the parent structure. Where the parent structure was part of a highly active combination, this would create strategic difficulties. The end-point of such a study would be a response rate that would have to be compared to the response rate of adriamycin in the same clinical situation. It would be unfair to compare the response rate of an analog used as tertiary drug treatment in breast cancer to that of adriamycin used in previously untreated patients. For each adriamycin-responsive tumor it will be necessary to determine (1) when an analog should have phase II evaluation; and (2) what response rate would indicate (a) little possibility of superiority to adriamycin in phase III; (b) probable comparable activities to adriamycin; or (c) probable superior activity to adriamycin.

The other two possibilities for an analog are much more simple to test for: if the desired end-point is activity in an adriamycin-unresponsive tumor, then a phase II study can be undertaken in previously untreated colorectal cancer, renal cancer, and malignant melanoma. Any level of meaningful activity would indicate the advisability of phase III trials. If the possible analog effect is lack of cross-resistance, the strategy just mentioned also includes this concept. Another approach is to take tumors responsive to adriamycin, after relapse on the drug, and to utilize the analog. Again, any meaningful response rate would be a positive result.

Phase III trials for new analogs have to be designed according to the effect being sought. One effect would be increased efficacy at a comparable level of toxicity. The second would be diminished cardiac toxicity at least at a comparable level of efficacy. The first effect requires the usual phase III approaches utilized with cytotoxic chemotherapy. Ideally this would involve some controlled comparison of the analog, either alone or in combination, with adriamycin. The potential for diminished cardiac toxicity requires a more innovative approach, which should utilize the endomyocardial biopsy technique.

With an anthracycline analog, the crucial end-point will not be the total dose of drug alone, but the total number of courses that can be administered. The new American drug AD-32 has a recommended dose schedule for phase II trials of 600 mg/m^2 every 3 weeks. If cardiotoxicity were observed at a total dose of 1800 mg/m^2, it could be said that AD-32 is less toxic to the heart than adriamycin, since more than three times the

Table 3. Hypothetical end-points of phase II studies

Toxicity[a]	↑	Efficacy[b] —	↓
Acute ↑ Cardiac ↑	Maybe	No	No
Acute ↑ Cardiac —	Yes	Maybe	No
Acute ↑ Cardiac↘	Yes	Yes	Yes
Acute ↘ Cardiac ↑	Maybe	No	No
Acute ↘ Cardiac —	Yes	Yes	Maybe
Acute ↘ Cardiac ↑	Yes	Maybe	No
Acute — Cardiac ↑	Maybe	No	No
Acute — Cardiac —	Yes	Maybe	No
Acute — Cardiac ↑	Yes	Yes	Maybe

[a] Toxicity
↘ Evidence that toxicity could be less than observed for adriamycin
— Evidence that toxicity is comparable to that of adriamycin or there are not enough data to allow a meaningful decision
↑ Evidence that toxicity could be more pronounced than observed for adriamycin
[b] Efficacy
Evidence that activity is superior to that observed with adriamycin
— Evidence that activity is comparable
↓ Evidence that activity is less pronounced than that observed with adriamycin

Table 2. Cardiac toxin comparisons possible between adriamycin and analog

Adriamycin		Analog	
No. of courses	Total dose (mg/m^2)	No. of courses	Possible biopsy changes sought
4	240	4	≥ 50% with normal biopsies
8	480	8	≥ 25% with normal biopsies
12	720	12	≤ 75% with 3+ changes
16	960	16	≤ 50% with 3+ changes

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