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*Review*

# Anthracycline analogs: The past, present, and future

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## Introduction

Doxorubicin (Adriamycin, Adria Laboratories) has the widest spectrum of antitumor activity of all chemotherapeutic agents and is used with a high degree of efficacy in many human cancers. It is probably the most utilized antitumor drug worldwide, and a majority of patients needing systemic treatment for cancer receive doxorubicin (DOX) at some time during their clinical course. The major obstacle to its use is its cumulative dose-limiting cardiotoxicity. Great effort has been expended to discover means of ameliorating, preventing, or at least delaying the onset of this cardiotoxicity. One method has been to create DOX analogs that cause less cardiotoxicity. Concomitant with this search for less cardiotoxic analogs is a search for analogs that may be administered orally or that have greater antitumor efficacy, especially for human cancers such as melanoma and colon carcinoma that are insensitive to DOX.

In the last decade a number of anthracycline analogs have been synthesized or isolated. One of these agents (epirubicin) has been developed to the point where it is commercially available in Europe and Canada. Others are undergoing clinical trials.

Developments in this field of anthracycline analogs are rapid and sometimes confusing. Many new analogs have been placed in clinical trial and others have been dropped because of inferiority in various respects. We review in depth four of these analogs (epirubicin, esorubicin, idarubicin, and menogaril) that are of current high interest and then review in a briefer fashion analogs in disuse and those with promise for the future.

### *Historical development of anthracyclines*

In the mid-1950s, Farmitalia Research Laboratories of Milan, Italy, initiated a program to study anticancer compounds produced by novel strains of microbes isolated from soil [51]. This effort began as an outgrowth of work in the U. S. successfully isolating the actinomycins, a group of compounds that interfered with cell division and had antitumor efficacy. In 1957, a colony of *Streptomyces* that produced a red pigment was grown from a soil sample collected at the Castel del Monte, near the city of Andria in southeastern Italy. This microbe produced an antibiotic that was named daunomycin (Daunii was the name of a pre-Roman tribe in southeastern Italy). Antitumor activity of this new agent was demonstrated in preclinical testing by Di Marco et al [35] in 1963.

At about the same time, Dubost and colleagues at the French firm of Rhône Poulenc, S. A. isolated an antitumor substance that they named rubidomycin (derived from rubis, the French word for ruby [42]. In 1963–1964, clinical testing of both agents was initiated in their respective countries of origin, and antitumor responses were seen in a variety of cancers, especially acute myelogenous leukemia [105]. By 1967, French clinical investigators began observing acute and chronic cardiac toxicity produced by rubidomycin [74, 89]. Rubidomycin and daunomycin were found later to be the same substance, and the designation was changed to daunorubicin (DNR).

The Farmitalia group (led by Di Marco and Arcamone) began inducing mutations of the new *Streptomyces* species *(S. peucetius)* hoping to create variant strains that might produce other useful antibiotics [51]. One strain had a blue-green color in its aerial mycelium and was named variety *caesius* for this color [51]. A new compound, 14-hydroxydaunomycin, was produced by this *Streptomyces* subspecies [51] and it was named Adriamycin, after the Adriatic Sea which is only a few miles from the site where the original soil sample had been collected.

Antitumor activity of this new drug in animal systems was demonstrated by 1968 [36]. Some of these studies indicated greater activity for Adriamycin than DNR. Adriamycin was quickly introduced into clinical trials in 1968 at the Istituto Nazionale Tumori in Milan by Bonadonna and proved to be highly active [13]. Studies in the United States began soon thereafter, and the remarkable antitumor efficacy observed by Bonadonna was confirmed [101]. In 1974, only 6 years after initial clinical use, the U. S. Food and Drug Administration approved Adriamycin (DOX) for marketing.

There is a difference of only a single hydroxyl group between the chemical structures of DNR and DOX, molecules with otherwise very complex structures. Yet, despite only a minor difference in chemical structure, there is a marked difference in their antitumor efficacy. For example, DOX is active against a wide spectrum of carcinomas and sarcomas, but DNR has little activity in such cancers [105].

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The clinical success of DOX and this disparity in spectrum of antitumor effect resulting from a minor molecular change has been the impetus for a diligent search for other effective or less toxic anthracycline analogs. The creation of analogs with less acute toxicity and/or less chronic cardiac toxicity has been a particular goal of investigators at Farmitalia. Three of the analogs (epirubicin, esorubicin, and idarubicin) to be discussed were developed by this group.

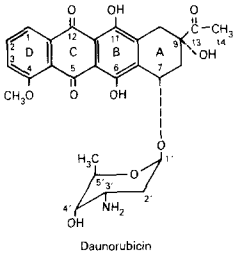
The Upjohn Co. of Kalamazoo, MI has been instrumental in developing another anthracycline analog, menogaril. Menogaril is a semisynthetic derivative of the naturally-occurring anthracycline antibiotic, nogalamycin, which is produced by *Streptomyces nogalater*. This organism had an odor in culture of black walnuts. The name was derived from *nogal*, Spanish for walnut and *ater*, Latin for black or dark. Nogalamycin was evaluated as an antitumor agent 20 years ago but was discarded as being too toxic [79]. In the mid-1970's the Upjohn Co. initiated a program for modifying the parent compound in an attempt to create a clinically useful analog. One analog synthesized, 7-*con*-*O*-methylnogarol (later renamed menogaril), had striking antitumor efficacy in animal systems [79]. In 1984 it was brought into clinical trials under joint Upjohn and National Cancer Institute sponsorship.

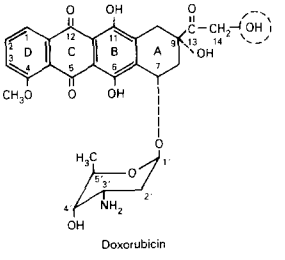
### Analog creation and development

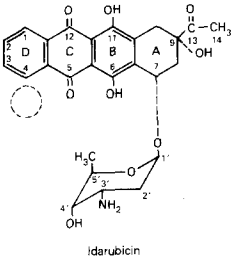
Anthracycline analogs have been both obtained from fungi isolated from soil samples and rationally synthesized. An example of the former is the discovery of carminomycin by Soviet Union investigators. This antibiotic was derived from the mycelia of a new actinomycete species isolated from a random soil sample [50]. A variation on this method is to subject the parent *Streptomyces* organism to various techniques that induce mutations and genetic code modifications so that random new compounds are created. This procedure was used to create DOX from a mutant strain of the *Streptomyces* that originally produced DNR [51]. The ability to synthesize DOX de novo has facilitated chemical modifications at the biologically active sites on the parent molecule [5]. The DOX analogs under discussion were created in this manner.

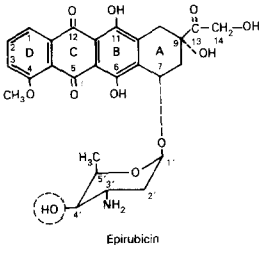
Many modifications have involved the C-9 side chain of the anthracyclines (Fig. 1). There are several reasons for this [3]. First, substitutions at this site are relatively easy to accomplish chemically. Second, substitutions on the C-14 methyl group create DOX derivatives such as esters and substituted amine analogs. Third, this side chain is probably not involved in important drug-receptor interactions. Fourth, the minor, and critical, change in the molecule that created DOX from DNR occurred at the C-14 site on this side chain.

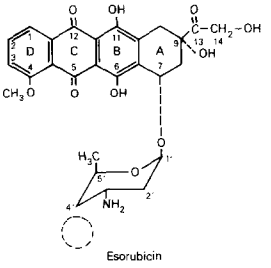
Another major site for modifications has been the aminosugar side chain at C-7 (Fig. 1). This aminosugar in the structure of DNR and DOX was named daunosamine when it was first identified [4]. Analogs developed by modifying the sugar moiety could have great therapeutic promise, because tissue distribution, cellular uptake, and intracellular distribution of the anthracyclines depend on the



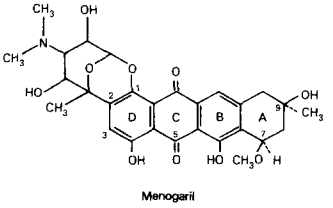




**Fig. 1.** The chemical structures of the anthracycline analogs under discussion. The *dotted circles* on the analogs of daunorubicin indicate the sites of differences

structure and stereochemistry of the carbohydrate side chain [3]. Analogs with isomeric configurational differences from the parent anthracyclines and analogs with structural changes have both been synthesized.

The third major area of structure modification has been in the anthraquinone rings. Variations in these parts of the molecule could modify the stability of the anthracycline-DNA complex, the selectivity towards receptor molecules, or the redox potential [3]. Ring D has been the site of most modifications because of the simplicity of such structure modification during synthesis of the parent compound.

Chemists have synthesized in excess of 1000 anthracycline analogs, but only a very few have undergone clinical testing. All such new compounds are first evaluated for antitumor efficacy in preclinical systems, and many are discarded at this step because of inferior activity compared to DOX [26]. If equivalent antitumor activity is seen, the agent is then tested for cardiotoxicity in rodents in equiactive antitumor doses and equimyelotoxic doses. Some are discarded at this stage as offering no advantage, either qualitatively or quantitatively, in toxicity, especially cardiotoxicity.

The criteria for selection of a new analog for clinical testing are superior preclinical antitumor activity to doxorubicin and no greater cardiotoxicity or at least equivalent antitumor activity and less cardiotoxicity. Unique physical properties, such as the possibility of oral administration, would also generate interest in an analog. The biologic activity of the antitumor anthracyclines is related to their ability to complex with DNA and cause inhibition of enzymes required for DNA replication and transcription. Thus, DNA synthesis and repair and RNA synthesis are compromised. New analogs of interest must also be nearly equivalent to DOX in their ability to bind DNA and to inhibit DNA and RNA synthesis [38].

## Epirubicin

One of the most extensively developed analogs thus far is epirubicin (EPI). It is now marketed in Canada and Europe under the trade name Farmorubicin. A New Drug Application has been submitted to the Food and Drug Administration for marketing in the U. S.

Arcamone and colleagues reported the synthesis of this analog in 1975 [5, 6]. It is the archetype of the analogs created by configurational changes in the daunosamine. It is an epimer of DOX which has an equatorial instead of an axial configuration of the hydroxyl group in the C-4' position[1] (Fig. 1). Except for this positional difference in a single hydroxyl group, it is structurally identical to DOX.

It was selected for further development because its preclinical antitumor efficacy was equal to DOX, and it had less cardiotoxicity in several animal species [5, 27, 54]. Studies using in vitro human tumor cell cloning assays indicated that the cytotoxicity of EPI was equivalent to that of DOX and was not qualitatively different [27, 54]. Similarly, comparative studies in transplantable mouse tumor lines showed that EPI had antitumor activity equivalent to or greater than DOX is nearly all systems [27]. The same was true in human tumor xenograft testing. Cardiac toxicity studies were performed in several rodent species [27, 48]. Histopathological studies in rabbit hearts indicated qualitative similarities of cardiac damage between EPI and DOX, but a quantitative scoring system demonstrated a 25% lesser degree of toxic effect for EPI [28]. Similar histological comparisons of cardiac toxicity in mice also showed a significant reduction of toxicity with EPI [48]. Other studies, using the isolated guinea pig heart, cultured mouse heart cells, and ECG testing comparisons in rats, uniformly demonstrated lesser degrees of cardiotoxicity from EPI, although cardiac effects still occurred [5, 28, 48]. These observations of equivalent antitumor activity and reduced cardiac toxicity compared to DOX indicated a promising advantage in therapeutic index for EPI.

Phase I clinical testing of EPI began at the Istituto Nazionale Tumori in 1977 [15]. Two years later U. S. clinical testing was initiated at Memorial Sloan Kettering Cancer Center [94]. The schedule chosen for phase I trials was bolus drug administration at 21-day intervals. The most commonly employed schedule for DOX was used for its analog.

The tolerable dose level achieved in both studies [15, 94] was 70–90 mg/m$^2$, with the lower dose being used for patients with compromised marrow reserve. Myelosuppression was dose-related with blood count nadirs occurring about 10 days after each dose, identical to the effect of DOX. However, compared to the effects of DOX there were fewer episodes of nausea and vomiting and fewer patients with marked alopecia.

### *Pharmacokinetics*

Although there appears to be little difference in antitumor efficacy in animals between EPI and DOX, the epimerization of the hydroxyl group at C-4' seems to cause differences in their pharmacokinetics. Studies in both animals and man have demonstrated that the metabolism and excretion of EPI are different from DOX, a possible explanation for the differences in toxicity [48].

Biliary excretion is the main route of elimination for both EPI and DOX and their metabolites. Hepatobiliary metabolism studies in rats showed that lesser amounts of unchanged EPI are excreted, whereas more reduced metabolite (4'-epi-doxorubicinol or epirubicinol) is excreted, compared to DOX [19]. These studies indicate that EPI is more extensively metabolized than DOX. Weenen et al. [103] studied the pharmacokinetics of patients treated with EPI and compared the results to reports of similar DOX analyses. They showed that EPI is also rapidly metabolized in human beings and that the terminal elimination phase is about one-half that of DOX. Robert and colleagues [90] also observed this faster plasma clearance of EPI.

EPI may be eliminated more quickly because it forms large quantities of metabolites by glucuronidation of the daunosamine moiety. Weenen and co-investigators [104] have shown that EPI and epirubicinol form glucuronides that are excreted in the urine. In contrast, DOX is not metabolized into such glucuronides. Formation of glucuronides facilitates the excretion process of many substances [104].

[1] The carbon atoms in the daunosamine are designated with a prime notation to differentiate them from the carbon atoms in the rest of the molecule.

**Table 1.** Antitumor responses to epirubicin

| Cancer | No. of patients evaluable | No. of patients responding[a] | Response rate (%) | References |
|---|---|---|---|---|
| *Breast* | | | | |
| Single drug (no prior CT) | 25 | 15 | 60 | 14, 62, 92 |
| Single drug (prior CT) | 122 | 29 | 24 | 14, 16, 23, 62, 63, 92 |
| Combination (CEF) | 82 | 37 | 45 | 2 |
| *Non-Hodgkin's lymphoma* | | | | |
| Single drug (no prior CT) | 11 | 10 | 91 | 73 |
| Single drug (prior CT) | 18 | 11 | 61 | 2, 16, 22, 23, 73 |
| *Colorectal* | | | | |
| Single drug (no prior CT) | 60 | 1 | 2 | 59, 80, 81, 106 |
| Single drug (prior CT) | 69 | 1 | 1.4 | 59, 80, 81, 106 |
| *Melanoma* | | | | |
| Single drug (no prior CT) | 40 | 3 | 7.5 | 10, 102 |
| Single drug (prior CT) | 25 | 1 | 4 | 10, 72, 102 |
| *Soft tissue sarcomas* | | | | |
| Single drug (no prior CT) | 75 | 11 | 15 | 84 |
| *Hepatocellular* | | | | |
| Single drug (no prior CT) | 18 | 3 | 17 | 58 |
| *Renal* | | | | |
| Single drug (no prior CT) | 13 | 0 | 0 | 47 |
| Single drug (prior CT) | 8 | 0 | 0 | 47 |
| *Gastric* | | | | |
| Single drug (no prior CT) | 24 | 4 | 17 | 93 |
| *Pancreatic* | | | | |
| Single drug (no prior CT) | 34 | 8 | 24 | 107 |
| *Non-small cell lung* | | | | |
| Single drug (no prior CT) | 42 | 3 | 7 | 65 |
| Single drug (prior CT) | 33 | 1 | 3 | 65 |

CT, chemotherapy; CEF, cyclophosphamide, epirubicin, 5-fluorouracil
[a] Complete + partial responses

### *Phases II and III studies*

A large number of phase II studies with EPI have been completed during the past 6 years. Some trials randomized patients to treatment with EPI vs DOX or another anthracycline. EPI has shown antitumor activity in a broad spectrum of malignancies similar to DOX (Table 1). A few phase III trials incorporating EPI in combination regimens also have been conducted.

*Breast Cancer.* EPI has been tested as a single drug in trials comparing its activity to other anthracyclines (Table 1). Most studies involved patients who had received either no prior chemotherapy or treatment with a regimen not containing an anthracycline. The therapeutic results from several studies are pooled in Table 1. The response rate in patients who had received prior chemotherapy was much lower than among patients who had not. The doses of EPI used in these studies varied from 75 to 90 mg/m$^2$ [14, 62, 63, 92].

The randomized comparative trials of EPI vs DOX in advanced breast cancer at the doses chosen indicate that the response rates are equivalent [14, 61, 63]. A few patients treated initially with EPI were later treated with DOX when their cancers progressed [92]. However, only one of 12 patients so treated responded, suggesting that there is cross-resistance between these two drugs, but the

small number of patients studied limits the validity of this point.

The combination of cyclosphosphamide, DOX, and 5-fluorouracil (CAF) produces the highest response rate and best survival in metastatic breast cancer [22], and this regimen is probably the one most widely favored for this stage of disease. Substitution of EPI for DOX in this regimen (CEF) has been compared to CAF in a randomized trial conducted in France [2] in patients who had not received prior chemotherapy for advanced disease (Table 1). The doses of each drug were equal in the two regimens; the dose of each anthracycline was 50 mg/m$^2$. The response rates for CEF (45%) and CAF (43%) were identical, as were the mean duration of response and the number of complete remissions. Thus, whether used as first-line or second-line treatment, as a single agent or in an effective combination regimen, EPI appears equivalent to DOX in antitumor activity for metastatic breast cancer.

*Other cancers.* Table 1 lists selected studies employing EPI in other tumors. EPI is active in the same tumors (e.g., lymphoma, sarcoma, hepatoma) and inactive in the same tumors (colorectal, melanoma, renal) as DOX. As in breast cancer, a randomized trial of EPI vs DOX, using equal doses in 150 patients with advanced soft tissue sarcomas [84], demonstrated that the two analogs had equivalent antitumor efficacy; the response rate for DOX was 24% and for EPI 15% ($p=0.21$). In a crossover treatment analysis only two of 24 patients failing to respond to EPI responded to DOX [84], again suggesting that cancers are generally cross-resistant to these two drugs.

*Toxicity.* It is clear that EPI and DOX have a similar spectrum of antitumor activity. EPI is an effective substitute for DOX in the treatment of breast cancer when used either as a single agent or in the CEF combination. If the two drugs have equal efficacy, EPI must provide a meaningful advantage in its toxicity spectrum to be useful clinically.

There have been at least five studies [2, 14, 61, 63, 84] in which the two analogs were prospectively and randomly compared. These trials provide the best means to compare acute and chronic toxicities. Table 2 outlines the five studies. It is important to note the drug doses used in each trial and to remember that equimyelotoxic doses for EPI are approximately 20 mg/m$^2$ greater than DOX [15, 63, 94].

In some of the uncontrolled phase II studies, EPI appeared to cause less alopecia and vomiting than DOX [10, 16, 73]. Table 2 provides details concerning toxicity of these two compounds in randomized comparisons. There is variability in the frequency of alopecia and vomiting, which may be partly due to differences in the investigators' definitions of what constitutes "severe" degrees of either side effect. However, in only two studies [2, 84] was there a statistically significant difference, and in these studies the differences could be explained by the fact that equimolar doses of the drugs were used rather than equally myelotoxic doses. The studies by Jain and colleagues [63] and Hortobagyi et al. [61] were the only ones that employed equally myelotoxic doses, and in both studies there were no differences in acute toxicity between the two agents.

The frequency of acute and chronic cardiac effects was also similar (Table 2), and the numbers of patients sustaining serious toxicity were small for both drugs. Jain et al. [63] showed that the median cumulative dose prior to development of cardiotoxicity was much higher for EPI than DOX, a variance that cannot be accounted for solely by the 25 mg/m$^2$ higher scheduled dose of EPI. Also, although episodes of congestive heart failure occurred from both drugs, the dose range at which this occurred was 456–600 mg/m$^2$ for DOX and 1035–1234 mg/m$^2$ (twice as much) for EPI [63].

**Table 2.** Randomized trials of doxorubicin vs epirubicin: comparison of toxicities

| Trial design | Drug dose and schedule | No. of patients | No. of patients with | | | | Reference | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | Severe alopecia | Vomiting | Acute cardiotoxicity | Chronic cardiotoxicity[a] | | |
| DOX | 75 mg/m$^2$ q21d | 21 | 100% | 72% | 4 | 5 | 14 | Percentage change in instrument testing of cardiac function was greater for doxrubicin |
| EPI | 75 mg/m$^2$ q21d | 21 | 100% | 53% | 4 | 2 | | |
| DOX | 60 mg/m$^2$ q21d | 29 | 35% | 67% | – | 5 | 63 | Median dose to development of cardiotoxicity for EPI was 935 mg/m$^2$, for DOX 468 mg/m$^2$ |
| EPI | 85 mg/m$^2$ q21d | 25 | 50% | 58% | – | 4 | | |
| DOX | 75 mg/m$^2$ q21d | 75 | 37% | 94% $p=0.05$ | 2 | 2 | 84 | |
| EPI | 75 mg/m$^2$ q21d | 75 | 26% | 77% | 0 | 2 | | |
| DOX | 60 mg/m$^2$ CI q21d | 16 | | | – | 3 | | |
| EPI | 90 mg/m$^2$ CI q21d | 24 | "Similar" | "Similar" | – | 2 | 61 | |
| EPI | 90 mg/m$^2$ bolus q21d | 18 | | | – | 3 | | |
| CAF DOX | 50 mg/m$^2$ q21d | 66 | 63% $p=0.001$ | – | 3 | 4 | 2 | |
| CEF EPI | 50 mg/m$^2$ q21d | 75 | 33% | – | 0 | 0 | | |

CI, continuous infusion × 48 h; EPI, epirubicin; DOX, doxorubicin; CAF, cyclophosphamide, doxorubicin (Adriamycin), 5-fluorouracil

[a] Defined as biopsy or instrument test finding of cardiac dysfunction indicative of cardiomyopathy, or congestive heart failure

*Comments*

The increase in therapeutic index for EPI suggested in the preclinical studies has been partially validated in clinical studies. There seems little doubt that EPI has a spectrum of antitumor activity that is qualitatively and quantitatively equivalent to DOX. It is less certain that there is an advantage in reduced acute toxicity when the two agents are administered in doses that produce equivalent myelotoxicity. Doses lower than maximally tolerated levels for either agent are associated with fewer acute side effects.

The study by Jain et al. [63] is pivotal in assessing any advantage for EPI with regard to cardiotoxicity. Using their data, one can calculate that a patient theoretically could receive three more doses of EPI than DOX before there is a high risk of cardiomyopathy[2]. This additional time on treatment could be beneficial to patients whose metastatic cancers are responding. If EPI were used as adjuvant therapy, concern for chronic cardiotoxicity would be reduced because this form of treatment is usually administered for only 6 months or fewer. Adjuvant therapy studies of primary breast cancer using EPI are in progress in France.

EPI's advantage in therapeutic index over DOX is modest, but apparently real. Whether the agent will be approved for marketing in the U. S. is not known; at present its use is restricted to clinical trials.

**Esorubicin**

Arcamone and coworkers have synthesized analogs with other modifications of the daunosamine moiety. In 1976 they reported [7] the synthesis of an analog in which a hydroxyl group is deleted from the C-4' position (Fig. 1). This compound was initially named 4'-deoxyadriamycin by Arcamone and was subsequently designated deoxydoxorubicin. Its adopted name is now esorubicin (ESO), a derivation from its Italian language name, 4'-d*eso*ssidoxorubicina. With the exception of the hydroxyl group deletion from C-4', it is structurally identical to DOX.

The initial antitumor testing of this agent in animals indicated a possible advantage over DOX [7] and further studies were pursued. Casazza et al. [31] compared ESO to DOX and found that ESO was generally equivalent to or more potent than DOX against various mouse tumors and was notably more active in colon 38 adenocarcinoma. The weekly treatment schedule appeared to be the most effective [31].

Others [52, 53, 87] have also observed activity of this agent in murine colon cancer lines. DOX-resistant human colon cancer xenografts have responded to ESO [52], and so have carcinogen-induced colon cancer lines [87]. In comparison with 5-fluorouracil and carmustine (BCNU), ESO was more active than either agent in xenografts of human colon and rectal cancers [53]. Such leads suggested that ESO might have activity against human colon cancer. If this were borne out in clinical trials, ESO would be a particularly interesting analog, because DOX and EPI are inactive in this cancer.

Cardiotoxicity studies of ESO also heightened interest in this analog. Casazza and colleagues [29] tested various doses of DOX, EPI, and ESO in rabbits using chronic dosing schedules. At equimyelotoxic doses, ESO caused no heart lesions whereas DOX caused marked histological abnormalities in the heart. In comparison to DOX and EPI, studies by the same group [29] showed that ESO also caused much less cardiotoxicity in mice. There are two possible mechanisms responsible for the lesser cardiac toxicity. One possibility is the inability of ESO to inhibit the fast-exchanging calcium compartment in myocardium [82]. Alternatively, ESO does not generate oxygen-containing free radicals [34], which may be a mediator of anthracycline cardiotoxicity.

ESO was introduced into phase I studies in 1982 under the joint sponsorship of the National Cancer Institute and Adria Laboratories, the U. S. subsidiary of Farmitalia Carlo Erba. Two dosing schedules were tested, every 21 days and weekly, primarily the former [45, 91, 96, 98].

ESO has a lower $LD_{10}$ (8.5 mg/kg) in mice than DOX [49] and the $LD_{50}$ at 30 days of ESO was about one-third that of DOX [29]. Thus, initial doses in the phase I trials were 5–20 mg/m$^2$, with the lower dose being used in the weekly schedule. Dose escalations to about 30 mg/m$^2$ given at 21-day intervals and 17.5 mg/m$^2$ given weekly were achieved, and these doses were recommended for phase II trials [45, 49, 91, 96, 98]. Slightly lower doses (25 mg/m$^2$ and 15 mg/m$^2$ respectively) were recommended for patients with limited marrow reserve [49, 96, 98]. Acute toxicity in the phase I trials paralleled that of DOX as far as myelosuppression was concerned, but there was appreciably less gastrointestinal disturbance and alopecia [45, 49, 91, 96, 98]. Two instances of premature ventricular contractions were observed [49], but these were not clearly drug-induced. Otherwise, no acute cardiac events were seen. There was no evidence of cumulative cardiotoxicity in a group of six patients who had total ESO doses of 200 mg/m$^2$ or more [45].

Although antitumor responses occur infrequently in phase I trials, Ferrari et al. [45] saw partial remissions in six of the 43 patients who received a drug dose near the maximally tolerated level. Responses occurred in patients with breast and colon cancers, among others.

*Pharmacokinetics*

Formelli and colleagues [46] compared the pharmacokinetics of ESO and DOX in mice and observed that ESO was cleared from tissue (including the heart) faster than DOX at both equimolar doses and equivalent antitumor doses. This more rapid clearance of ESO was also seen in clinical studies. Stanton et al. [98] found that ESO had a rapid initial clearance, but then a very prolonged terminal elimination phase. The initial phase clearance was significantly more rapid than DOX [98]. In contrast to EPI, there is limited metabolism of ESO to the alcohol metabolite, esorubicinol [39]. As discussed earlier with regard to EPI, the reduced toxicity from ESO seen in preclinical studies may also be a function of decreased exposure to the drug.

*Phase II studies*

A number of phase II trials have been started, but many are not yet completed. Phase III evaluations have not been started, pending completion of phase II trials. Published trials to date are summarized in Table 3. Adequate numbers of patients have been analyzed in only non-small cell lung cancer and possibly colon cancer. There were no responders in patients with either cancer. Responses in pa-

[2] Assuming 100% dose each course and using the median dose to development of cardiotoxicity (63), one could give eight courses of DOX (468 ÷ 60 = 8) and 11 courses of EPI (935 ÷ 85 = 11)

**Table 3.** Antitumor responses to esorubicin

| Cancer | No. of patients evaluable | No. of patients responding | Response rate (%) | References |
|---|---|---|---|---|
| *Breast* | | | | |
| Single drug (no prior CT) | 4 | 0 | 0 | 71 |
| Single drug (prior CT) | 40 | 5 | 12.5 | 18, 71 |
| *Colon* | | | | |
| Single drug (no prior CT) | 20 | 0 | 0 | 60 |
| Single drug (prior CT) | 45 | 0 | 0 | 60 |
| *Non-small cell lung* | | | | |
| Single drug (no prior CT) | 94 | 0 | 0 | 68, 88 |
| Single drug (prior CT) | 7 | 0 | 0 | 68 |

CT, chemotherapy

tients with breast cancer (Table 3) have occurred [18], but the published data thus far suggest that the response rate is inferior to that obtained with DOX.

Toxicity has been compared to that produced by DOX and the other analogs. Alopecia and vomiting have occurred much less often with ESO than DOX [18, 68, 71]. Bonfante and colleagues [18] noted significant changes in cardiac ejection fractions in four of 24 patients; none of these 24 patients had received an anthracycline previously. Three other patients (G. Sarosy, National Cancer Institute, personal communication) have had cardiac function abnormalities after a cumulative dose of at least 150 mg/m$^2$.

*Comments*

The published data are too scanty to draw conclusions yet about the efficacy of ESO. However, it does appear that the promise of efficacy in colon cancer, portended by the preclinical data, has not been fulfilled.

Cardiotoxicity appears possible with ESO, but the frequency and severity have not yet been determined. ESO definitely produces less toxicity that causes patient distress (alopecia and vomiting), but unless antitumor efficacy is nearly equivalent to DOX, ESO will offer no improvement in therapeutic index and probably will not be studied further.

**Idarubicin**

The perfection of techniques for de novo synthesis of anthracyclines allowed the creation of analogs with modifications of the D ring in the anthraquinone moiety. In 1976 Arcamone and colleagues [8] synthesized new derivatives of DNR in which the methoxyl group at the C-4 position in ring D was deleted. Preclinical testing for antitumor activity indicated that one of these analogs, the anomer of 4-demethoxy-daunorubicin, was worthy of further evaluation [100]. Subsequently, this analog was designated idarubicin (IDA), a derivation of its Italian language name, 4-demetoss*ida*unorubicina. The lack of the methoxyl group is its only structural difference from DNR (Fig. 1).

Animal tumor studies compared the activity of IDA to the parent DNR. At doses 4–8 times lower than DNR, IDA had an equal or greater activity in L1210 leukemia and Gross leukemia [8]. It also had a markedly superior inhibitory effect on cultured HeLa cells at lower concentrations compared to the parent compound [100]. Investigations of the uptake in mouse embryo fibroblasts demonstrated that IDA uptake was much faster than that of DNR [100]. The greater antitumor activity of IDA at lower concentrations may be related to this fact. DNA synthesis in mouse fibroblasts was inhibited equally by the two compounds [100].

Di Marco, Casazza, and colleagues [30, 37] investigated the antitumor activity of orally administered IDA based on the hypothesis that the different spectrum of antitumor activity of this agent was related to a different pharmacological behavior. Supino et al. [100] had demonstrated that IDA had a higher affinity for lipids than the other analogs which suggested that good oral absorption was possible. At an oral dose approximately 3.5 times higher than the intravenous dose, oral IDA had activity in various murine leukemias equivalent to that of intravenous DOX or DNR [30, 37]. This was a salient observation, because an anthracycline that is effective orally would be a more convenient antitumor agent to use. In contrast, orally administered DOX and DNR are, respectively, inactive and less active in murine systems than intravenously administered drug [37].

Phase I studies of IDA were begun in 1980 [17]. Both the oral and intravenous routes of administration have been tested. The doses intially used were 1.5 mg/m$^2$ intravenously and 6 mg/m$^2$ orally. The higher oral dose corresponded to the observations of Di Marco et al. [37] that a 3.5 times greater dose orally was necessary to achieve antitumor efficacy equivalent to that of the intravenous route. This dose difference is possibly related to inefficiency in gastrointestinal drug absorption, but other factors may also play a role. Schedules tested were a single dose every 21 days and a daily dose $\times 5$ days. The maximally tolerated single dose for treatment of solid tumors was 12 mg/m$^2$ intravenously and 40 mg/m$^2$ orally [9, 17, 57, 67]. The recommended intravenous dose for treatment of acute leukemia is 10 mg/m$^2$ daily $\times 3$ days [33].

Toxicities noted in the phase I studies paralleled those of DNR. Myelosuppression was the dose-limiting toxicity,

**Table 4.** Antitumor responses to idarubicin

| Cancer | No. of patients evaluable | No. of patients responding[b] | Response rate (%) | References |
|---|---|---|---|---|
| *ANLL* | | | | |
| Single drug (prior CT)[a] | 46 | 8 | 17 | 24, 33 |
| Combination (prior CT)[a] | 1 | 1 | 100 | 70 |
| Combination (no prior CT) | 10 | 10 | 100 | 25 |
| *Colorectal* | | | | |
| Single drug (no prior CT) | 14 | 1 | 7 | 56 |
| Single drug (prior CT) | 29 | 0 | 0 | 56 |
| *Esophageal/gastric* | | | | |
| Single drug (no prior CT) | 12 | 1 | 8 | 44 |
| Single drug (prior CT) | 13 | 0 | 0 | 44 |
| *Melanoma* | | | | |
| Single drug (no prior CT) | 11 | 0 | 0 | 99 |
| Single drug (prior CT) | 3 | 0 | 0 | 99 |
| *Renal* | | | | |
| Single drug (no prior CT) | 14 | 0 | 0 | 95 |
| Single drug (prior CT) | 5 | 0 | 0 | 95 |
| *Ovarian* | | | | |
| Single drug (prior CT) | 17 | 0 | 0 | 55 |
| *Non-small cell lung* | | | | |
| Single drug (no prior CT) | 18 | 0 | 0 | 66 |
| Single drug (prior CT) | 2 | 0 | 0 | 66 |
| Single drug (oral) (no prior CT) | 11 | 0 | 0 | 69 |
| Single drug (oral) (prior CT) | 19 | 0 | 0 | 69 |
| *Breast* | | | | |
| Single drug (oral) (prior CT) | 25 | 7 | 28 | 75 |

Intravenous route unless otherwise specified
ANLL, acute nonlymphocytic leukemia
[a] Includes prior anthracyclines in most patients
[b] Complete + partial responses

**Table 5.** Selected toxicities observed from idarubicin in patients having no prior chemotherapy

| Reference | No. of patients | Patients with vomiting (%) | Patients with noticeable alopecia (%) | No. of patients with acute cardiac effects |
|---|---|---|---|---|
| 56 | 14 | 0 | 0 | 0 |
| 99 | 11 | NR | 0 | 0 |
| 95 | 19 | 43 | 10 | 0 |
| 66 | 20 | 40 | 30 | 1 |

NR: The trial included previously treated and untreated patients; the degree of side effect was not recorded for the patient cohort with no prior treatment

with leukopenia being more common than thrombocytopenia [9, 17, 33, 57, 67]. Alopecia occurred in only one-third of patients or fewer [9], in contrast to the nearly uniform total alopecia that occurs from either DOX or DNR. The oral route caused a higher incidence of alopecia than the intravenous route in one study [9] but the opposite was true in another study [17]. The oral preparation caused significantly more vomiting than the intravenous route of administration [9, 17], and dividing the oral dose over 3 consecutive days did not assuage this side effect [9].

Minor acute electrocardiographic abnormalities were observed in one study [17], again with the oral route causing a greater incidence than the intravenous one. The patients in this study were monitored for cardiac events by performing ECGs serially over several hours after drug administration. Chronic cardiotoxicity effects were also monitored in this trial by means of serial echocardiograms, but no changes were seen in the few patients who received median cumulative drug doses of 72 mg/m$^2$ intravenously and 262 mg/m$^2$ orally [17].

*Pharmacokinetics*

IDA is metabolized to a reduced alcohol, idarubicinol , in the liver [20]. Preclinical pharmacokinetic studies by Broggini and coworkers [20] indicate that IDA forms significantly lower amounts of the reduced alcohol than does DNR and also has a much slower elimination rate. The slower elimination is probably due to the lower alcohol metabolite formation. In testing IDA via both the oral and intravenous routes, Broggini et al. [20] observed that this analog is retained in tissues and tumor in higher concentrations and for longer half-lives than DNR, with a higher accumulation in tumor tissue than heart and spleen. Oral administration provided the highest tumor to organ concentration ratio [20]. These observations imply that the pharmacology of IDA will provide it with a therapeutic advantage over DNR and that the oral route should be the more favorable one.

Clinicopharmacologic studies also demonstrated prolonged drug elimination and retention of the idarubicinol metabolite [9, 33]. Idarubicinol has equivalent antitumor efficacy to IDA in murine tumor systems [32]. This slow elimination and antitumor efficacy of a metabolite suggest that IDA could be a particularly potent anthracycline.

*Phases II and III studies*

IDA has undergone extensive trial in disease-oriented studies. Table 4 lists the results from selected reports.

DNR is highly active in acute leukemia and is an essential component in the initial treatment of acute leukemia, especially the nonlymphocytic type. In contrast, it has little or no activity in carcinomas [105]. The preclinical studies with IDA that suggested a therapeutic advantage over DNR have, so far, not been borne out in the clinical trials. Although the patient numbers are generally small in the trials listed in Table 4, the results from these studies suggest that IDA will not have an antitumor spectrum different from that of DNR. A possible exception is breast cancer.

All but two of the trials listed in Table 4 used the intravenous route of administration. The oral route of administration has promise for greater antitumor efficacy, but most ongoing phase II trials using it are not yet complete, and to date only two studies [69, 75] have been reported.

The complete remission rate in patients with ANLL who have had prior treatment (almost always including DOX or DNR) is 17% (Table 4). These data suggest that there may be some lack of cross-resistance between IDA and the parent analogs. However, the patient numbers are low, and this point needs further clinical testing. If this is confirmed, then leukemia regimens for future testing might include both agents; for example, intravenous DNR in the induction therapy and oral IDA as part of maintenance therapy.

There is as yet no well-defined efficacy advantage of IDA over DNR. Therefore, differences in toxicity become important. There have been no randomized comparisons of the two agents similar to those conducted of EPI vs DOX. However, the spectrum of reported acute and chronic toxicities has been similar to that of DNR [9, 17, 24, 33]. Table 5 lists the degree of selected toxicities in those trials utilizing IDA as initial and sole chemotherapy. Alopecia, if it occurs at all, is mild in degree, and vomiting is also mild, occurring within several hours of drug administration in 20%–40% of patients [56, 66, 95].

There are also no randomized prospective comparisons of the two routes of administration for IDA, but Bonfante et al. [17] compared the two routes in alternate patients consecutively. At dose levels producing approximately equal degrees of myelosuppression, the oral route caused more vomiting than the intravenous one. Others [9] have also noted such a difference. These results suggest that the only remarkable toxicity advantage for IDA over DNR is less alopecia. The emetic effect also appears to be less, but this advantage may be forfeited when the drug is administered orally.

*Comments*

The therapeutic advantage of IDA over DNR appears to be marginal so far. There are leads that suggest some lack of cross-resistance between these analogs in acute leukemia and therapeutic activity of IDA in breast cancer. The increase in efficacy predicted by the preclinical studies has not been demonstrated so far in the clinical trials. However, there has not been sufficient evaluation of oral IDA, nor have randomized comparisons of the two analogs been done. A multi-institutional group in the USA has recently begun a randomized trial comparing the two drugs, each in combination with cytosine arabinoside, as initial therapy in acute myelogenous leukemia.

Differences in toxicity between IDA and DNR are also marginal. One advantage of IDA, less alopecia, may be lost if the drug is used in combination with other antitumor agents. Both agents cause isolated instances of minor acute cardiac effects. Too few patients have been treated with cumulative IDA doses high enough to assess cardiomyopathy risks adequately.

**Menogaril**

The main impetus for development of the three previous analogs has been the need for an agent with equal antitumor efficacy to, but less cardiotoxicity than, DOX. Other investigators have pursued a different direction and have emphasized development of analogs predicted to have better antitumor activity than DOX through either a greater antitumor spectrum or less generation of resistance. A secondary, but still important, interest is less toxicity. Wiley

**Table 6.** Miscellaneous anthracyclines and their current status

| Name of drug | Current status |
|---|---|
| Aclarubicin (aclacinomycin) | Marketed in France and Japan. Phase II testing generally complete, clinical trials closed in U.S.; no clear advantage over DOX. Studies being pursued regarding activity as a cell maturation inducer [83] |
| AD-32 | Initial clinical trials indicated drug formulation problems and toxicity [12]. No plans for further development |
| Carminomycin | Used in Russia and Eastern Europe. Phase II testing generally complete; no clear advantage over DOX. Clinical trials closed in U.S. |
| 3'-Deamino-3'(3-cyano--4-morpholinyl)doxorubicin | Most potent doxorubicin analog in animal tumors yet synthesized [1]; in preclinical evaluation |
| 4-Demethoxy-4'-*O*--methyldoxorubicin | High antitumor activity, no cardiac toxicity, activity via oral route in animal tumors [86]; in preclinical evaluation |
| Detorubicin | Clinical trials being phased out in Europe and U.S. Synthesis is difficult, no advantage over DOX |
| 5-Iminodaunorubicin | Has reduced cardiotoxicity [64]; in preclinical evaluation |
| Marcellomycin | Phase I trials completed in Europe; myelosuppression was erratic [85]. No plans for further development |
| 4'-*O*-Tetrahydropyranyl adriamycin | In phase II testing in Japan and Europe [76]; clinical trials in U.S. to begin soon |
| Zorubicin (rubidazone) | Clinical trials closed in the U.S.; no advantage over DOX |

et al. [108] found that the nogalamycin analog menogaril (MEN) had superior antitumor activity in P388 leukemia compared to DOX and some 20 other nogalamycin analogs and selected it for further study. The major difference in chemical structure between MEN and other anthracyclines is that in MEN the aminosugar is connected to ring D and is attached via both carbon-oxygen and carbon-carbon bonds (Fig. 1). There are several other lesser differences too.

A variety of antitumor efficacy studies in preclinical systems indicate that MEN has a spectrum of activity similar to that of DOX [79]. The only differences are that MEN is more active in colon tumor lines, and it is inactive in the human breast cancer xenograft. Moreover, MEN has antitumor activity when administered orally [77], which indicates a potential advantage for MEN over DOX. There is suggestion of possible cross-resistance in that MEN was inactive against DOX-resistant P388 leukemia [77].

The biochemical mechanism of action of MEN appears to differ from the previously discussed anthracyclines. MEN accumulates in the cytoplasm, whereas DOX accumulates in the nucleus [11]. MEN binds weakly to DNA, in contrast to DOX, and the two drugs also differ in their cell cycle effects [79].

The cardiotoxic potential of MEN was evaluated in rabbits by McGovren and coworkers [78]. Cumulative drug doses of 2640–3700 mg/m$^2$ produced nonfatal, characteristic anthracycline lesions in the heart, whereas fatal cardiomyopathy occurred in control rabbits given DOX at cumulative doses of only 7%–10% of the MEN level. Since the optimal antitumor dose of DOX in preclinical studies is 8%–20% of the MEN dose, it may be possible to use MEN for a longer interval than DOX before cardiomyopathy becomes evident [78].

Phase I trials of intravenous MEN were begun in 1984, and several schedules were studied [21, 40, 41, 79, 97]. Two dose schedules have been recommended for phase II trials: (a) 160–200 mg/m$^2$ on day 1; (b) 140 mg/m$^2$ on days 1 and 8. Both schedules are repeated every 28 days, because the white blood cell count nadir occurs at about day 16. No antitumor activity was seen in these phase I trials [21, 40, 41, 97].

The dose-limiting toxicity is leukopenia. Other toxicities include anemia, mild to moderate alopecia, nausea and vomiting, and moderate to severe phlebitis at the infusion site [21, 40, 41, 97]. The latter problem was mitigated in one study [41] by keeping the infusion concentration under 1 mg/ml. Brown et al. [21] did ECG monitoring for 24 h during and after drug administration and observed no acute cardiac effects. Two patients received a cumulative drug dose of 1340–1500 mg/m$^2$ and had no change in cardiac function as determined by serial gated scans [21, 41].

### *Pharmacokinetics*

The major metabolic pathway of MEN is via demethylation of the aminosugar instead of the glucuronidation and alcohol formation that occurs with DNR, DOX, and the other analogs [43]. Pharmacokinetic studies of MEN showed two significant differences from DOX and the other analogs: a) only a small percentage of MEN fluorescent metabolites are present in plasma; b) no major route of drug clearance is through urinary or biliary excretion of parent drug and its fluorescent metabolites [97]. The precise route of clearance has not yet been determined.

### *Phase II studies*

A number of institutions and cooperative groups began phase II trials in 1985 with intravenous MEN, and phase I trials with the oral route have also recently begun.

### *Comments*

Since phase II trials have just begun, it is premature to assess the merits of MEN relative to other anthracyclines under discussion or comment on its antitumor efficacy. Because of the possible cross-resistance of MEN with other anthracyclines, virtually all ongoing phase II trials exclude patients who have been previously treated with an anthracyline.

## Other anthracyclines

Table 6 is an account of anthracyclines that have undergone clinical testing over the past decade or may in the near future. Some of these are commercially available in some countries but not in the USA. Some have been tested clinically, but their present status can be characterized as "inactive", meaning that there are no plans for further development (at least in the USA) because they have no advantage over DOX. Others that demonstrate advantages in preclinical testing will go to clinical trial in the near future.

Laboratories in Europe, Japan, and the USA are continuing to synthesize new anthracycline analogs. Some are discarded after preclinical testing and others have extensive clinical trials before it is determined that they have no advantage over DOX and/or DNR and are discarded.

### *Comments*

In this review we have surveyed the current status of anthracycline analog development. However, we have not addressed some of the more fundamental preclinical and clinical dilemmas. Is the current murine screen an efficient means of identifying compounds with either increased potency or activity? Will the new in vitro human clonogenic or nonclonogenic systems prove to be better? Are the current human xenograft lines efficient predictors of clinical activity? Do the current animal cardiotoxicity models predict for relative grades of clinical toxicity?

At the clinical level, the definitive question of whether more prolonged schedules lead to an improved therapeutic index has not been answered. The efficiency in screening new analogs at the phase II level has been improved considerably. However, randomized phase III trials still need work in the definition of exact endpoints for cardiotoxicity. Also, designs assessing true clinical cross-resistance patterns are rather weak.

At this time, the only adequately evaluated analog to demonstrate an apparent advantage over DOX is EPI, and this advantage is the modest one that it can be administered repetitively for a slightly longer time. The outlook for ESO is not optimistic, as present trials suggest no advantage in therapeutic index compared to DOX. The outlook for IDA is still uncertain; it may have a role in the treatment of certain malignancies. Presently, most studies involve use of the intravenous formulation. No potential advantage of the oral formulation is yet being explored at the phase III level. MEN is just entering disease-oriented trials, and no predictions about its future are possible. Although no clear-cut clinical advantage has yet been defined for any of these analogs, it is hoped that the success of Di Marco and colleagues in discovering DOX (a "better DNR") can be repeated by others searching for a "better DOX".

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