ONCHEM 00003

New anthracycline antitumor antibiotics

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Contents

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I. Abstract

Doxorubicin is an essential component of the treatment of aggressive lymphoma, childhood solid tumors, bone and soft tissue sarcomas, and breast cancer and additional indications are emerging. On the other hand, daunorubicin has occupied the central position of interest in the treatment of acute leukemia. Epirubicin has a spectrum very similar to doxorubicin but lesser toxicity. The ability to protect against cardiotoxicity with ICRF-187 further enhances clinical interest in exploiting modifications in doze intensity to therapeutic advantage. Idarubicin has at least equivalent activity to daunorubicin and doxorubicin in leukemia.

New areas of research in relation to anthracycline antibiotics include introduction of new the analogs, insight into mechanisms of resistance, the reversal of multidrug resistance in vitro, the protection of cardiac toxicity, and the study of other important biochemical reactions relevant to cytotoxicity.

Orally active anthracyclines such as idarubicin and compounds which lack cross-resistance with the parent drugs or have other mechanisms for cytotoxicity are being developed. It is likely that these modifications will lead to an expanding therapeutic spectrum for these already widely useful drugs.

II. Introduction

This review updates the status of anthracycline research concentrating on the clinical prospects of drugs that have been introduced following the first decade of clinical anthracycline studies (1965–1975). The interest generated by daunorubicin and doxorubicin in cancer treatment has been documented in several previous comprehensive overviews, and also in proceedings of scientific meetings which have coupled advances in basic and clinical knowledge on anthracyclines as anticancer drugs [1–8]. A recent volume edited by J. William Lown covers in detail the following aspects: (i) isolation, synthesis and properties, (ii) biophysical studies related to mechanisms of action, and (iii) pharmacology, toxicity and clinical aspects of these compounds and the synthetic anthracenediones. For the clinician desiring a perspective on new anthracycline antibiotics, we shall focus on new compounds which are in clinical trial, while also summarizing important new directions in anthracycline research. Accordingly we shall begin with an overview of anthracycline drug development in order to provide the appropriate background and the rationale for the interest generated by these drugs; continue with a summary of new findings still being acquired with the parent compounds in the clinic, and then proceed to an individual description of each new agent. This sequence logically leads to an appraisal of future prospects in cancer treatment.

III. Overview of anthracycline drug development

III-A. Historical Background

Anthracycline antibiotics were isolated and studied in various pharmaceutical laboratories since the late 1950s and early 1960s. Most prominent in this effort were the group at the Farmitalia Research Laboratories in Milano headed by Aramone and DiMarco [9] and the Parisian group of the Rhone-Poulenc Laboratories whose anthracycline research was developed by Dubost et al. [10]. The Italian group first embarked in clinical studies with 'daunomycin' and subsequently its C-14 hydroxy derivative 'adriamycin', whereas the French concomitantly initiated clinical studies with 'rubidomycin'. These drugs were soon renamed 'daunorubicin' (upon demonstration of the chemical identity of daunomycin and rubidomycin) and 'doxorubicin'. Interest in other laboratories followed quickly with new related chemical structures being studied in the United States, Germany, the Soviet Union and Japan [11]. Some of these com-

pounds differed substantially in structure and in toxicologic properties, and were eventually introduced into clinical trial (see Section V).

The initial clinical studies with daunorubicin both in France and the United States provided the impetus for further interest in anthracycline drug development: impressive activity was noted against acute leukemia and childhood solid tumors, but a vast array of toxicities including marrow hypoplasia, total alopecia, extravasation necrosis and a peculiar cardiomyopathy became evident [12,13]. Trials with doxorubicin, in large part sponsored by the National Cancer Institute (NCI, U.S.A.) began to demonstrate impressive activity in breast cancer, ovarian cancer, malignant lymphomas, small cell lung cancer, germ cell tumors and sarcomas in addition to the areas where daunorubicin already had established efficacy [1]. The success of doxorubicin blunted further development of daunorubicin [14] and also of second generation derivatives such as rubidazone [15].

Groups at Farmitalia and at Stanford Research Institute became particularly active in structure-activity relationships and dissected out important toxicologic features and determinants of potency [16,17]. Several of these compounds, which are derivatives of doxorubicin (DX) or daunorubicin (DNR) have been readied for clinical trial and will be covered in Section V. Only preclinical data is currently available for other compounds which are targeted for clinical development such as the 3′,3-cyano-4-morpholinyl derivatives, with their unique 1000-times potency relative to DX [17,18].

Anthracycline drug development also became established at the Institute of Microbial Chemistry in Tokyo, where the trisaccharide aclacinomycin was the first readied for clinical trial [19]. Biochemical effects on nucleolar RNA synthesis of this drug and others isolated by Bristol Myers (e.g., marcellomycin, musettamycin) were distinct enough from DX and DNR that a classification evolved in Type I and Type II anthracyclines depending on their effects on RNA vs. DNA synthesis inhibition [20]. At the Upjohn Company, derivatives of another anthraquinone, nogalomycin, were studied [21] and in 1984 they introduced menogaril into clinical trial. Additional drugs tested included a compound developed by Israel at the Dana Farber Cancer Institute (AD-32) [22]; this compound and other water soluble derivatives are being considered for subsequent clinical trial. More recently, other derivatives closely related to doxorubicin: THP-adriamycin (THP-DX) and detorubicin were introduced in Japan and France, respectively [23,24].

Finally, there have been many attempts at developing carriers for several of the anthracyclines. These carriers have included calf thymus DNA [25], ferrous iron [26],

amino acids [27], various types of liposomes [28], neutral phosphalipids [29] and conjugates with monoclonal antibodies [30]. Such attempts to improve targeting and attenuate toxicity have met with varying degrees of success. Ultimately, they have not become established treatment methods because practical issues have not been resolved. While searches for better and less toxic analogs have continued, increasing knowledge about mechanisms of action has led to important therapeutic concepts of drug synergy and resistance, and has stimulated efforts on other methods of protecting against toxicities of established anthracyclines. These will be described further in the next heading. Table 1 and Fig. 1 indicate the structures that have been developed for clinical study.

III-B. General concepts

Table 2 summarizes biological effects and biochemical targets of anthracycline antibiotics. Based on effects on DNA vs. RNA synthesis inhibition the classification proposed by DuVernay and Crooke introduced the terms Type I and Type II anthracyclines [20]. Such classification usually separates monosaccharides from di- and trisaccharides, and does not address the multitude of other biochemical mechanisms associated with anthracycline action. New compounds are introduced with specific properties in mind. For example, 4-iminoDNR lacks a quinone moiety which precludes free radical activation [28]. Cyanomorpholynyl derivatives are considerably more potent than parent compounds, bind irreversibly to DNA, and show a lack of crossresistance [18]. Changes in the 4′ position have been exploited by Arcamone and co-workers at Farmitalia Carlo Erba [16]. The stereoisomer of DX by an inversion at the C-4′ position has resulted in the 4′-epi derivative with attenuated toxicity and allowing unique glucuronide formation as a metabolite. The 4′-deoxy derivative (esorubicin) was introduced because of even greater attenuation in toxi-

TABLE 1

Clinically treated anthracyclines

Idarubicin (4-demethoxydaunorubicin)
Epirubicin (4′-epidoxorubicin)
Esorubicin (4′-deoxydoxorubicin)
4′ iodo-4′ deoxydoxorubicin
Rubidazone
Carminomycin (4-demethyldaunorubicin)
THP-Adriamycin (4′-O-tetrahydropyranyl doxorubicin)
AD-32
Aclacinomycin A
Detorubicin
Menogaril

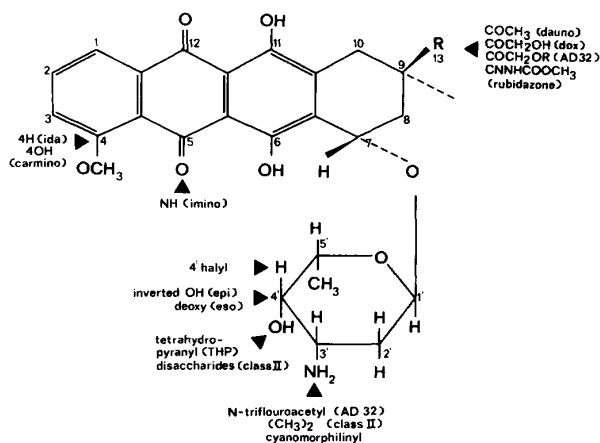Fig. 1. Structure of anthracyclines with identification of major analog classes in relation to chemical substituents.

TABLE 2

Biological and biochemical effects of anthracyclines binding to DNA

Inhibition of topoisomerase II
Inhibition of DNA polymerases
Induction of DNA breaks
Free radical generation
Cell membrane disruption
Ion exchange alterations
Binding to phospholipids, calmodulin

city [6]. Although clinical studies have not indicated sufficient activity for this last compound, the addition of halogens at the 4' position (4' iodo 4' deoxyDX) results in enhanced potency, oral activity and activity against P388 DX-resistant leukemia [18,31].

Replacement of the methoxy group in the 4 position (4-demethoxy derivatives) have yielded idarubicin which is active orally and appears of interest in leukemia (Section IV) [32]. Carminomycin is a demethoxy anthracycline which is considerably more potent than DX or DNR but with lesser activity [5]. Additional compounds containing 6-deoxy and 11-deoxy modifications will lead to further information on structure-activity relationships [18].

A-ring side arm changes were among the first being explored (in fact DX is the first such derivative of DNR) [15]. Other side chain derivatives include rubidazone, detorubicin and AD-32, the latter also having an N-trifluoroacetyl linked to the amino sugar [33–36].

This last modification is shared by other AD series compounds synthesized by Israel which have lesser potency and toxicity, and do not appear to intercalate in the nucleus [33–36]. A different chromophore that in addition has a sugar originating in the D-ring rather than in the A-ring is menogaril [21]. This compound has shown attenuated toxicities and is in clinical trial (Section V).

Differential action on the immune system is yet another property on which to base structure-activity relationships [37]. However, the contribution of such effects on the ultimate antitumor action is uncertain.

III-C. Specific research areas

The diversity of anthracycline actions has spawned a

wide variety of research directions, some representing general trends in analog development and others which are unique to the anthracyclines. Section IV includes newer trends in the use of doxorubicin, whereas Section V deals with some findings with analogs which have already become established in the clinic.

III-C. 1. Expanding therapeutic spectrum

More active drugs are always desirable, but often unattainable as the first discovered compound is often the most strikingly active of the series. More potent compounds have been commonly identified but this does not necessarily indicate better antitumor activity. Compounds which might be more effective against leukemia such as 4-demethoxyDNR (idarubicin) provide valuable clues with regards to selectivity of anthracyclines. In leukemia, DNR and its derivatives are at least equally active if not better than DX [38]. It remains to be seen whether drugs with very different mechanisms of action will have an altered therapeutic spectrum. Aclacinomycin's activity appeared confined to leukemia, whereas little is known on selectivity of compounds such as cyanomorpholino derivatives. Selectivity towards colon cancer was claimed for esorubicin [39], however, subsequent trials were disappointing.

III-C. 2. Attenuating toxicities

Subjective tolerance may be improved in anthracyclines that are prodrugs of the parent compounds, presumably because these are equivalent in part to slow release forms. For example, rubidazone may be less toxic than DNR, and THP-DX has been claimed to be less toxic than DX. Subjective tolerance is often reflected by diminished nausea and vomiting, lesser stomatitis, lesser alopecia and more consistent myelosuppression as dose-limiting toxicity. Claims have been made for menogaril, THP-DX, aclacinomycin, and AD-32 in causing less alopecia [40]; epirubicin was also milder in all these aspects, but also may have less myelosuppression than DX at doses which are believed to be equivalent in efficacy [41].

A specific effort has been made to attenuate the car-

diotoxicity of these drugs by utilizing animal screens [42]. Some claims were later not substantiated in clinical studies (e.g., the lack of cardiotoxicity of carminomycin and of esorubicin). Clinical experience has validated the lesser cardiotoxicity of epirubicin which is presumably related to its more favorable pharmacology. Based on clinical findings to date, menogaril appears less cardiotoxic, and similar claims have been made for AD-32 and THP-DX from preliminary phase I data. (Section V and its references.)

Aclacinomycin trials and results of phase I studies with marcellomycin have suggested a different toxicity spectrum for these trisaccharides: considerable nausea and vomiting, more erratic and delayed myelosuppression, and a tendency to give rise to acute arrhythmias even though cardiomyopathy and extravasation necrosis were absent. Preclinical studies in Japan had suggested that aclacinomycin was not mutagenic in systems where DX was very mutagenic. Such finding had been considered a rationale for further testing, including adjuvant situations, but unfortunately efficacy was found wanting in solid tumors.

In summary, attenuated toxicities are a justification for the development of some of these analogs. With the exception of epirubicin, however, the antitumor spectrum of most analogs is substantially different from DX. Therefore, one cannot consider such analogs merely as less toxic DXs, but other circumstances for their use may be found. For example, intraperitoneal therapy with AD-32 and aclacinomycin may be considered appropriate, whreas DX is too toxic via this route. In some instances not only is lesser efficacy a problem with these analogs, but new toxicities appear. Several compounds have local toxicities rendering peripheral vein administration problematic (e.g., esorubicin, AD-32, menogaril).

III-C. 3. Favorable pharmacology

Activity via the oral route may be a useful property with obvious advantages in patients with childhood leukemias and in breast cancer where compromised venous access is common. However, when oral trials have been performed, they have so far been accompanied by slightly more variable bioavailability and also by some gastrointestinal intolerance. Nevertheless, the oral route is being explored further with idarubicin and menogaril. This latter drug causes phlebitis so that oral administration may prove advantageous.

A vast amount of information is accumulating on comparative pharmacokinetics of anthracyclines [43]. Tissue distribution may account for the relative lesser toxicity claimed for THP-DX. Similarly, tissue and intracellular distribution is vastly changed with AD-32 and its derivatives. The lipophilicity of AD-32 required special solvents and 24 h infusion schedules. Liposomal carriers also greatly change the tissue distribution and may alter the toxicology of anthracyclines.

Metabolic degradation has common threads: bioreductive production of alcohols being the most important followed by a variety of sugar ring cleavages [44]. Such reductive products are generally less active than the parent compound, but in the case of idarubicin, the 13-(S)-alcohol derivative is actually more active and has a longer half-life [18]. The ratios of alcohol derivative to parent compound may be increased with oral administration for this drug.

Of great interest was the discovery of glucuronides as products of epirubicin metabolism. This stereoisomer of DX is more extensively metabolized and may account for its better tolerance. This pharmacologic property may also render it more suitable than DX for combinations with a cardioprotective agent (see item F, this section). Glucuronide formation is a unique property of human metabolism, not having been identified in preclinical studies.

III-D. Differentiating properties

Some evidence that anthracyclines promote differentiation has been acccrued, and it has stimulated interest in possible clinical implications. Studies have dealt primarily with Friends murine leukemia model and the human promyelocytic leukemia HL-60 [45]. Both in vitro and in vivo studies indicate varying contributions to differentiation among anthracyclines. Noteworthy has been the activity of marcellomycin in inducing differentiation in the various systems studies. However, more remains to be learned on how this action may be exploited. Combinations of anthracyclines with low dose cytosine arabinoside in myelodysplastic states are considered worth testing. The effect of 'differentiating' agents in solid tumor treatment is just beginning to be explored with several drugs in clinical trial. Anthracyclines may have actions on DNA and RNA synthesis which will prove useful in achieving such effects alone or in combination. At present, phenomena of teratoma derivation from embryonal cancers, and ganglioneuromas from neuroblastoma appear related in part to biochemical effects of drugs.

III-E. Intrinsic and acquired resistance

Drug resistance to antracyclines has been the central focus of much research since the laboratory discovery of multidrug resistance (mdr) to natural products [46]. Clinical counterparts of this phenomenon are not diffi-

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