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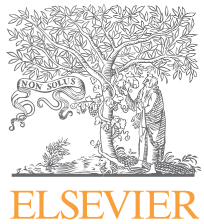

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Introduction

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ABSTRACT

Since their introduction in the 1960s, anthracyclines such as doxorubicin have attained a central place in the management of a number of solid tumours and haematological malignancies. Anthracycline-based regimens constitute a standard of care in patients with metastatic breast cancer; anthracycline monotherapy compares favourably with taxanes alone, while combinations of anthracyclines and taxanes have been shown to be superior to anthracycline-based regimens in terms of response rates and progression-free survival. Similarly, in patients with early breast cancer, adjuvant therapy with anthracycline-based regimens significantly reduces breast cancer mortality, compared with cyclophosphamide–methotrexate–fluorouracil regimens. However, a major limitation to the use of anthracyclines is cumulative cardiotoxicity, which can result in irreversible congestive heart failure. A number of strategies to reduce cardiotoxicity have been investigated, including modification of the dosing regimen, use of cardioprotective agents, and the development of liposomal doxorubicin formulations. The central place of anthracyclines in breast cancer management is likely to continue: the challenge now is to identify those patients most likely to respond to, and benefit from, anthracycline-based therapy.

1. Introduction

During the four decades since their introduction, anthracyclines have attained a central place in the treatment of breast cancer and other solid tumours and haematological malignancies. Anthracycline-based regimens currently represent a 'gold standard' for treatment of metastatic breast cancer,[1] and have a central place in the adjuvant therapy of early breast cancer.[2] Furthermore, our increasing understanding of the molecular biology of breast cancer is highlighting potential opportunities to maximise the clinical benefits of anthracyclines, for example by identifying patients who are most likely to respond to treatment.[3]

2. Historical perspectives

The anthracycline story began in 1960, when Federico Arcamone and coworkers filed a patent application for the "fermentative production and recovery of an antibiotic obtained from *Streptomyces krestomyceticus*". This approach bore fruit in 1963, when a novel cytotoxic compound derived from *S. peuceticus* was simultaneously isolated by researchers in Italy and France. The Italian group named this compound daunomycin after the Dauni, a pre-Roman tribe who lived in the Castel del Monte area where the research took place, while the French group named it rubidomycin in reference to its red colour. Elements from both names were combined to

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Table 1 – Progression-free survival, response rate and overall survival with taxanes and anthracyclines given as single agents, based on a meta-analysis of eight randomised trials. [1]

	Taxane single agent (n = 464)	Anthracycline single agent (n = 455)	P-value
Progression-free survival (months)	5.1	7.2	0.011
Response rate (%)	33	38	0.063
Overall survival (months)	19.5	18.6	0.91

Adapted with permission from Piccart-Gebhart MJ, et al. Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. *J Clin Oncol* 2008;**26**: 1980–6.

give the compound the name by which it is known today: daunorubicin. Subsequently, a hydroxylated derivative of daunorubicin was isolated by Arcamone's group and named adriamycin (a reference to the Adriatic Sea); it was later renamed doxorubicin to conform to the established naming convention. In preclinical studies, doxorubicin showed higher activity against solid murine tumours, and a higher therapeutic index, compared with daunorubicin. [4,5] Clinical evaluation of doxorubicin in both adults and children yielded promising results in a number of solid tumours, including rare or difficult-to-treat tumours. [5]

3. Clinical efficacy of anthracyclines in breast cancer

In 1977, Smalley et al. reported that an anthracycline-based regimen produced significantly higher response rates and a longer duration of response than a conventional cyclophosphamide-based regimen in patients with metastatic breast cancer. [6] These findings were subsequently confirmed in numerous studies, [7,8] which have established anthracycline-based regimens as a standard of care for patients with advanced breast cancer. Moreover, this position has been maintained since the introduction of the taxanes in the late 1990s. A meta-analysis of eight randomised trials, involving over 3000 patients, showed that single-agent therapy with anthracyclines produced significantly longer progression-free survival than taxanes alone, and a trend towards a higher response rate, in patients with metastatic breast cancer (Table 1). [1] Combinations of taxanes and anthracyclines were superior to anthracycline-based regimens in terms of response rates and progression-free survival, but not in terms of overall survival. [1]

Recent years have seen earlier detection of breast cancer, as a result of effective screening programmes, and this trend has focused attention on the use of adjuvant therapy in early disease. In 2003, a randomised trial involving almost 1000 patients with early breast cancer showed that the combination of doxorubicin, cyclophosphamide and 5-fluorouracil was superior to the conventional regimen of cyclophosphamide, methotrexate and 5-fluorouracil in terms of disease-free and overall survival, particularly in node-negative patients. [9] These findings were confirmed in a subsequent meta-analysis, which showed that anthracycline-based regimens significantly improved survival in women with early breast cancer, irrespective of nodal status and tumour characteristics. [10]

4. Managing anthracycline cardiotoxicity

The original clinical evaluation of doxorubicin, which involved 146 patients, identified alopecia, oral ulceration and myelosuppression as the principal toxicities associated with this agent. [5] However, it subsequently became apparent that anthracyclines are associated with cumulative cardiotoxicity, which can result in the development of congestive heart failure (CHF) (Fig. 1). [11] The incidence of CHF increases from 3% at a doxorubicin cumulative dose of 400 mg/m^2 to 18% at a cumulative dose of 700 mg/m^2. [12] A number of risk factors for cardiotoxicity have been identified, including previous exposure to anthracyclines, age, history of cardiovascular disease, and previous treatment with paclitaxel or trastuzumab. [12] Cardiotoxicity is also seen with newer anthracyclines, such as epirubicin. [13] It is the main factor limiting anthracycline treatment, particularly in patients with advanced disease, and can necessitate the withdrawal of treatment in patients who might otherwise continue to benefit.

Strategies to reduce anthracycline cardiotoxicity have involved modification of the dosage regimen, treatment with cardioprotective agents, and the development of liposomal doxorubicin formulations. As shown in Fig. 1, weekly treatment with low doses of doxorubicin can significantly delay the development of CHF, [14] allowing higher cumulative doses to be given, and administration by prolonged (48 or 96 hours) intravenous infusion rather than intravenous injection has also been shown to reduce cardiotoxicity. [15] However, these approaches are rarely used in clinical practice, especially when doxorubicin is used in combination with other agents.

Several studies have investigated the use of dexrazoxane, an iron-chelating agent that scavenges free radicals, as a means of limiting anthracycline-related cardiotoxicity. In an initial study in patients with

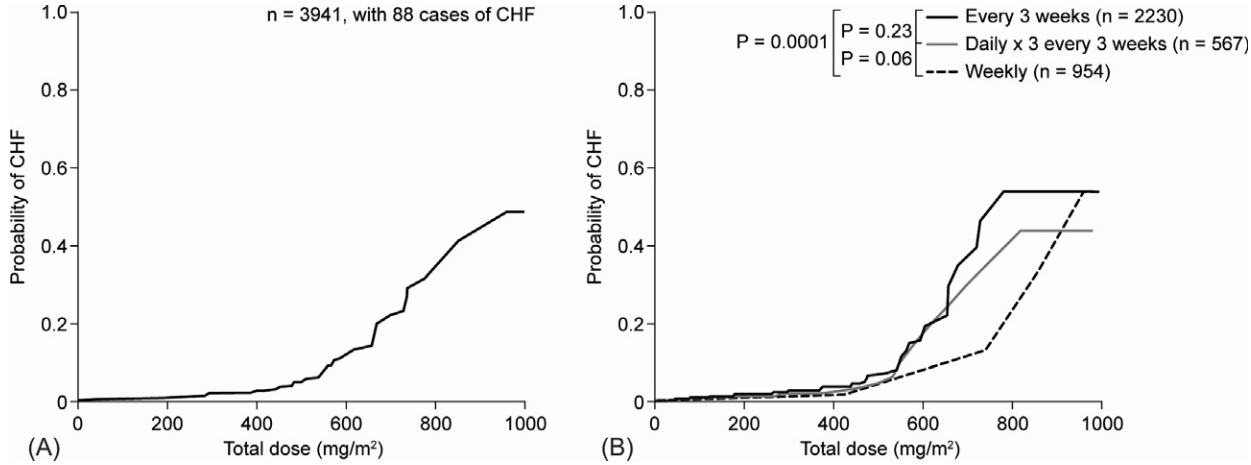

Fig. 1 – Risk of developing congestive heart failure (CHF) in relation to (A) the cumulative dose of doxorubicin and (B) the dosing regimen. [11] **Reprinted with permission from Von Hoff DD, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 1979;91:710–7.**

advanced breast cancer, patients receiving this agent tolerated significantly higher doses of doxorubicin than those receiving doxorubicin alone, and experienced less cardiotoxicity.[16] In this study, the response rate was lower in dexrazoxane-treated patients (37% vs 41%), which suggested a possible adverse impact on the antitumour efficacy of doxorubicin. However, a subsequent systematic review of nine randomised trials found that dexrazoxane significantly reduced the risk of CHF without affecting the response rate or survival, and hence the authors concluded that it should be considered in patients at high risk of cardiotoxicity.[17]

Two liposomal doxorubicin formulations are currently available: pegylated and non-pegylated. In a large prospective trial in patients with metastatic breast cancer, the risk of cardiovascular adverse events was significantly lower with pegylated liposomal doxorubicin than with the conventional formulation (11% vs 40%, respectively).[18] However, pegylated liposomal doxorubicin is associated with a significant risk of palmar–plantar erythrodysesthesia (hand–foot syndrome),[19] which may limit its usefulness in some patients. Non-pegylated doxorubicin liposomes are small particles, approximately 150 nm in diameter, from which the drug is preferentially released in tissues that are rich in phagocytic reticuloendothelial cells, such as the liver and bone marrow, rather than the heart. A systematic review of two randomised controlled trials with this formulation showed that non-pegylated liposomal doxorubicin (NPLD) was associated with a significantly lower rate of both clinical CHF and subclinical heart failure, compared with conventional doxorubicin.[13] Other studies have shown that combination therapy with NPLD and agents such as taxanes or trastuzumab results in high efficacy without an increase in cardiotoxicity.[20,21] Moreover, because this formulation does not accumulate in the skin or mucous membranes, it is associated with a lower risk of palmar–plantar erythrodysesthesia, compared with pegylated liposomal doxorubicin.

In addition to the strategies described above, much recent attention has focused on the use of predictive biomarkers to try to identify those patients who will respond to anthracycline therapy, as described by Di Leo et al. in this supplement. This would enable patients who would not benefit from anthracycline therapy to be spared the potential cardiotoxicity and other adverse effects associated with these agents.

5. Conclusions

After almost half a century, anthracyclines continue to occupy a central place in the management of breast cancer. This situation is likely to continue as evidence for the benefits of liposomal doxorubicin formulations – in terms of reducing cardiotoxicity – accumulates. The challenge now is to identify those patients most likely to respond to, and benefit from, anthracycline-based therapy.[2,3] This challenge was the theme of an international workshop, *Moving forward with new data and approaches: a fresh look at anthracyclines in breast cancer and NHL*, which took place in Meldola, Italy, in September 2010. This meeting reviewed recent data on the use of anthracyclines in the treatment of breast cancer and non-Hodgkin's lymphoma, with the aim of providing guidance on how the management of these diseases can be improved. The presentations on breast cancer at this meeting are summarised in this supplement.

6. Conflict of interest statement

Professor Amadori has received honoraria from Cephalon.

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