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Commentary

Cardiotoxicity of Anthracyclines

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(A COMMENT ON: KONNO T, MAEDA H, IWAI K *et al.* Effect of arterial administration of high-molecular-weight anticancer agent SMANCS with lipid lymphographic agent on hepatoma: a preliminary report. *Eur J Cancer Clin Oncol* 1983, **19**, 1053–1065.)

DOSE-RELATED cardiotoxicity does not allow the full exploitation of the antitumour activity of the anthracycline antibiotics. Von Hoff has demonstrated in two excellent studies an abrupt increase at high cumulative doses in the risk of developing clinical cardiac toxicity with the two most widely used drugs of this class, daunorubicin and doxorubicin. In large retrospective series of patients culled from the records of the major U.S. oncologic cooperative groups he demonstrated a limiting dose of 600 mg/m^2 [1] for daunorubicin and 550 mg/m^2 for doxorubicin [2]. However, the limitation of this empiric approach to stopping doxorubicin at this predetermined dose is highlighted by the fact that in the latter study, of the 185 patients who had the drug stopped at 550 mg/m^2 19% were in complete remission, 28% had achieved a partial remission and 34% had stable disease. The magnitude of the clinical problem is even greater when one considers the patients in whom doxorubicin is withheld because of potential cardiotoxicity when this drug would otherwise be the treatment of choice. This is particularly true in breast cancer, where the decision to apply the most active agent into adjuvant therapy must be balanced against the risk of cardiotoxicity in otherwise 'healthy patients'. Strategies to prevent the cardiotoxicity of the anthracyclines are hampered by the lack of understanding of the causative mechanism. Considerable progress has been made both in defining the pathologic changes in humans and in developing animal models of the cardiotoxicity. Billingham *et al.* have described the morphologic cardiac changes in chronic anthracycline toxicity and have introduced a numerical grading system [3]. These changes appear to be fairly characteristic of anthracycline toxicity and can be graded by the degree of myofibrillar dropout, swelling of the sarcoplasmic reticulum and total myocyte damage and necrosis. Furthermore, they can be accurately reproduced in a number of experimental animals [4–6]. Chronic anthracycline-induced cardiac lesions can be blocked by huge doses of antihistamines and beta blockers [7]; however, these animal trials have not been confirmed in man. Moreover, the pathological lesions induced by histamines and catecholamines tend to be focal, whereas those induced by anthracycline are more global. Therefore these agents may not be directly involved in this damage to the myocytes [8, 9]. Other histopathologic and electrophysiologic studies have revealed interstitial edema with increased intracellular calcium and sodium; however, calcium antagonists did not protect against toxicity [10].

Currently the favored mechanism of anthracycline cardiotoxicity is viewed as a free radical effect on the myocytes. There is ample evidence to support the generation of free radicals by anthracyclines. This has been shown to occur via a cytochrome P450 reductase-mediated reaction and the formation of a semiquinone radical intermediate [11–13]. The cytotoxicity is believed to occur mainly through a mechanism of lipid peroxidation causing marked damage to mitochondrial membranes and endoplasmic reticulum [12, 14]. It is of interest in the light of the pathologic observations of sarcoplasmic reticulum swelling and mitochondrial degeneration

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that both these organelles generate superoxide ions when exposed to doxorubicin [15, 16]. The heart is particularly susceptible to free radical damage, possibly because it has less superoxide dismutase and catalase activity than other tissues [17]. Moreover, doxorubicin directly depresses cardiac glutathione peroxidase activity, one of the major defenses against free radical damage [18]. An interesting aspect of free radical formation is the recent observation that doxorubicin can bind iron with an extremely high affinity [19]. The iron–doxorubicin complex has been shown *in vitro* to cause oxygen radical formation [20] and marked lipid peroxidation, while neither doxorubicin or iron alone cause this affect [21]. *In vivo* trials in mice and rats with the free radical scavengers alpha-tocopherol and *N*-acetylcysteine have shown cardioprotection without altering tumoricidal activity of doxorubicin [22, 23]. However, the trials with these agents in rabbits and most recently in man have not demonstrated this cardioprotection [24–26].

Based on this presumptive mechanism of action, three strategies have been used to overcome the cardiotoxicity problem: (1) the development of analogs; (2) alteration of schedule; and (3) development of cardioprotective agents. A number of anthracycline analogs have been entered into clinical trial. Some have shown promise [27, 28]; none to date have clearly demonstrated equivalent antitumor activity without cardiotoxicity. In our own studies with 4′-epiadriamycin, cardiotoxicity appears at a higher dose than that of doxorubicin but is still observed [29]. This approach is still attractive but awaits results of current trials and additional experience with some of the newer agents, particularly 4′-deoxydoxorubicin.

Schedule alteration is based on the hypothesis that cardiotoxicity is related to peak levels of the anthracycline while the antitumor activity is related to total drug exposure (i.e. the area under the concentration × time curve). There is *in vitro* evidence for the separation of cardiac and antitumor effects of the drug [22]. Furthermore, a number of retrospective studies [2, 30, 31] demonstrated that more frequent lower-dose schedules resulted in less clinical cardiac toxicity. These observations lead to trials with continuous infusion schedules ranging from 6 hr [32] to 96 hr [33] and even 60 days [34]. However, these studies, have led to data which must be interpreted with caution because of the different end-points used for the assessment of cardiotoxicity. For example, Legha *et al.* observed decreased injury as judged by endomyocardial biopsy in infusions of up to 96 hr [33] and Lokich *et al.* observed no evidence of clinical failure in prolonged infusions of up to 60 days [34]. At New York University Medical Center we tested 6-hr and 24-hr infusions [32]. Neither was completely protective when left ventricular ejection fractions (LVEF), as determined by nuclear gated pool scans, were used as a measure of cardiac function. In a subsequent study in patients with advanced breast cancer combining 6-hr infusions with bolus 5-fluorouracil and cyclophosphamide, antitumor efficacy was maintained but there was a clear trend for all patients to decrease their left ventricular ejection fraction to between 300 and 400 mg/m^2 [35]. It is essential for the interpretation of such studies to know the cardiac end-point and its specificity and sensitivity in comparison to other end-points used in the assessment of cardiotoxicity. Besides the increased expense and the slight morbidity involved in these studies, it is still too early to recommend this type of schedule outside of a well-constructed clinical study.

A trial of cardioprotective agents is attractive since it combines the extensive experience of a known active cytotoxic agent used in a convenient bolus administration schedule. This protection strategy also assumes separate mechanisms of cardiac and antitumor activity. It is amenable to the outpatient setting and does not necessitate the indwelling catheters and pumps required by the prolonged schedules. The most promising agents which have been investigated as doxorubicin cardioprotectors in preclinical systems have been ICRF-159 and its enantiomer ICRF-187, *N*-acetylcysteine [36], alpha-tocopherol [37] and coenzyme Q [38]. The only drug to enter a controlled clinical trial was *N*-acetylcysteine, which unfortunately did not provide cardioprotection in the schedule used [37].

The report by Konno *et al.* in a previous issue of the journal raises further questions about the mechanisms of anthracycline cardiotoxicity and introduces another agent as a possible cardioprotector. Clinical investigators need to persue these laboratory leads, since sensitive clinical monitoring is now available. Hopefully studies such as these will allow observations to be made which will give further insight into the mechanism of this major toxicity.

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