Preventing the cardiotoxicity of anthracyclines by dexrazoxane

A real breakthrough

Anthracyclines such as doxorubicin are among the most widely used anticancer drugs and are often given to children as part of curative regimens. Yet long term cardiac damage is a major adverse effect that limits the effectiveness of these drugs, particularly in children. The introduction of dexrazoxane to limit the cardiotoxicity of anthracyclines is a real advance in the treatment of some forms of cancer.

Cardiotoxicity induced by anthracyclines primarily affects the myocardium and is dose related, cumulative, and irreversible. Each dose of the anthracycline doxorubicin produces an increment of myocardial damage. The normal heart can compensate for this until a lifetime dose of some 450 mg/m^2 has been reached, after which the compensatory cardiac mechanisms begin to fail. In childhood malignancies, which may be cured if sufficient anthracyclines can be given, cardiotoxicity is more erratic and severe than in adults.[1] Each dose may unpredictably cause severe toxicity, or subclinical cardiotoxicity may become overt only in adolescence or early adulthood.[2] A way of preventing cardiotoxicity in children taking anthracyclines will therefore prevent not only the appearance of young iatrogenic cardiac cripples but also the need for the occasional heart transplantation.[3]

Since the anthracyclines, especially doxorubicin, are among the most active of anticancer drugs, intense research over the past 25 years has sought to find a way of preventing their cardiotoxicity. Attempts to find specific cardiotoxicity inhibitors that do not reduce the antitumour effect of anthracyclines or produce new adverse reactions have resulted in numerous claims, but none that has been substantiated in clinical trials—except for dexrazoxane. Doxorubicin's cardiotoxicity is thought to result from oxygen free radicals, production of which is catalysed by a doxorubicin-iron complex. Dexrazoxane, however, is a more potent chelating agent than doxorubicin and acts by removing the iron from the complex, thus preventing cardiac damage.[4] Dexrazoxane is currently the only clinically proved cardioprotective agent against anthracycline induced cardiotoxicity,[5–7] and it has now been licensed for use in many parts of the world, including North America, France, Italy, Ireland, Denmark, and all of eastern Europe, but no application for a licence has yet been made in the United Kingdom or Japan.

Some have questioned the need for cardioprotectants, arguing that the same objectives can be met by limiting the dose of doxorubicin and then switching patients to other drugs. With other chemotherapies, however, complete regressions—for example, in breast cancer—are few and patient survival short. This advice therefore not only hinders progress; it is also unethical because it is not in patients' interests to be switched from treatment that is effective to one that may not be. In their review of chemoprotective agents Phillips and Tannock rightly emphasise that patient benefit is the criterion by which these drugs ought to be judged.[8]

Sixteen published clinical trials, nine of them randomised, with definitive studies by Speyer et al[9] and by Swain et al,[10 11] have examined the role of dexrazoxane in combination with anthracyclines. The trials were carried out in seven countries and have included 2016 patients. All have shown that dexrazoxane is highly effective as a cardioprotectant. It prevents the cardiotoxicity of doxorubicin, epirubicin, and daunorubicin, thus allowing effective but potentially cardiotoxic treatment to continue beyond the maximum tolerated dose limit.[9–11] It does so without producing any new adverse effects, aggravating the side effects of anthracyclines (except for a slight increase in neutropenia), or reducing their antitumour efficacy.

One sequential analysis has shown that dexraxozane doubles the median overall survival time of patients with breast cancer responding to the FAC regimen (fluorouracil, doxorubicin, cyclophosphamide). These patients had already received 300 mg/m^2 of doxorubicin and were judged to be likely to benefit from further treatment with FAC. Median survival time for those who received FAC plus placebo was 460 days while for those receiving FAC plus dexrazoxane it was 882 days.[11] The use of dexrazoxane also reduced significantly the severity of the gastrointestinal toxicity of the FAC regimen.[10 11]

These results have implications for the more effective use of cancer chemotherapy. The use of dexrazoxane allows patients with pre-existing cardiac risk factors, such as cardiac abnormalities, hypertension, diabetes, age over 65, previous radiotherapy to the left breast or mediastinum, to receive the same cumulative dose of anthracycline as those with no risk factors.[9 11] Moreover, it may give patients who failed or became resistant to anthracyclines the opportunity of receiving full doses of second line cardiotoxic drugs—for example, mitoxantrone (or radiotherapy)—without fear of additive cardiotoxicity. And it may provide patients who relapse after initial treatment with an anthracycline the possibility of retreatment with the same dose of the same drug as they responded to originally.

Although in one trial in advanced breast cancer it seemed as though dexrazoxane had reduced the response rate to FAC, this reduction lacked both internal and external consistency. Assiduous but mistaken dissemination of this result has undoubtedly slowed the adoption of dexrazoxane—but regulatory authorities have not. In the United States the Food and Drug Administration gave dexrazoxane accelerated approval, while the Canadian authority designated it the only breakthrough drug among the 20 new drugs submitted to it in 1995.[12]

KH has received fees for speaking and attending a symposium from the manufacturers of dexrazoxane.

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HIV and tuberculosis in the Commonwealth

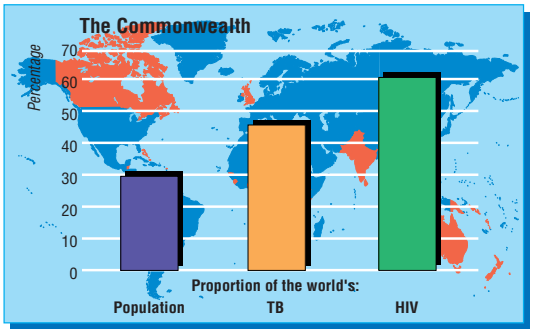
Heads of governments can learn from one another's successes

The countries of the Commonwealth share more than a common heritage of British rule. They also share a disproportionate burden of communicable disease, particularly HIV and tuberculosis. Yet there are also considerable success stories within Commonwealth countries in controlling these diseases—and these too should be shared. The Commonwealth heads of government meeting in Durban in November provides such an opportunity.

Though Commonwealth countries represent only 29.5% of the global population, they account for 60.5% of cases of HIV and 42.3% of those of tuberculosis (see figure and fuller table on www.bmj.com).[1 2] The total numbers involved are massive and reflect significant health burdens requiring substantial investments if their impact on health and development are to be mitigated.[1]

Yet some Commonwealth countries have shown important successes in controlling these diseases, and there is much that countries could learn from each other if some effort was put into organising the transfer of information and experience from one country to another. Uganda, for example, has shown remarkable openness and success in reducing HIV transmission, particularly among young people,[3] while the United Kingdom and Australia have done far better than most comparable industrialised countries in limiting the penetration of HIV after it first appeared in the early 1980s.[1 4] Equally, tuberculosis control programmes in several Commonwealth countries (Malawi, Kenya, and Tanzania) are model programmes which, at least until the advent of HIV, were achieving high population coverage and good cure rates.[2]

South Asia represents a particularly urgent case where lessons learnt in Africa could be usefully applied. India, Pakistan, Bangladesh, and Sri Lanka account for 72.0% of the population in the Commonwealth. Currently they account for only an estimated 22.2% of prevalent HIV in the Commonwealth, though at 71.3% of smear positive cases, tuberculosis is far better established (see table on www.bmj.com). Given the manner in which the emergence of HIV in Africa has fuelled tuberculosis epidemics, the risk is that HIV in India and Pakistan will cause a further explosion within already well established tuberculosis epidemics.[1 5] HIV remains an emerging infection worldwide, and what happens in south Asia, particularly India, will be crucial to the future course of the pandemic.[1]



As preventable infections whose impact can also be mitigated, HIV and tuberculosis must be prime candidates for discussion in any Commonwealth country concerned with health protection and health gain. The Association of Commonwealth Universities is hosting an expert meeting on HIV and AIDS in Durban immediately before the Commonwealth heads of government meeting in an attempt to draw its attention to the issues surrounding HIV (see www.bmj.com), and there is a strong case for these and other health related topics being on the agenda of the Commonwealth meeting.

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website *e*xtra

Table showing prevalence of AIDS and tuberculosis in Commonwealth countries appears on the BMJ's website

www.bmj.com

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