REVIEW

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The current and future role of dexrazoxane as a cardioprotectant in anthracycline treatment: expert panel review

Abstract This article summarizes the views of an expert meeting of cardiologists and oncologists on the use of dexrazoxane in anthracycline-based chemotherapy. Anthracycline-induced cardiotoxicity remains a major concern and new trends in treatment (e.g., combination of an anthracycline with other agents) will ensure that it remains a problem. Dexrazoxane reduces this cardiotoxicity in adults and children with a range of tumor types. Further research may help to identify those patients who are at particular risk of cardiotoxicity and who would benefit the most from dexrazoxane. There are also numerous possibilities for dexrazoxane in other clinical situations, which must be addressed in future trials.

Keywords Cancer · Anthracycline · Doxorubicin · Cardiotoxicity · Dexrazoxane

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Background and objectives

Due to their efficacy in a range of tumor types, anthracyclines such as doxorubicin remain important drugs for the oncologist. With the wealth of data concerning the cardiac effects of anthracyclines, cardiotoxicity has become a key factor in prescribing anthracyclines and in determining maximum cumulative dose. Of the various attempts to reduce the potential for cardiac damage, the only consistently effective one has been the cardioprotectant drug dexrazoxane. Although dexrazoxane is a topoisomerase II inhibitor (Sehested & Jensen 1996) and was originally developed as a chemotherapeutic agent, it showed insufficient efficacy in this respect.

A relatively small percentage of patients receiving anthracyclines are prescribed dexrazoxane, and dexrazoxane's use is inconsistent between different practitioners, different patient groups, and different countries. Some standardization of the treatment guidelines is therefore desirable.

This report reflects the consensus view of a meeting of cardiologists and oncologists held in Paris on 6 September 2001. The objectives of the meeting were to agree on recommendations for current dexrazoxane use, and to identify potential future indications for dexrazoxane which warrant further research.

Anthracycline-induced cardiotoxicity: how big is the problem?

Despite the availability of newer compounds, anthracyclines are still a mainstay of treatment for some of the most common tumor types, such as breast cancer. In childhood cancers, anthracycline use is very common: one study showed that over 50% of survivors of childhood cancer have received anthracyclines (Krischer et al. 1997). Anthracycline use for metastatic breast cancer has declined, probably reflecting an increased awareness of the cardiotoxicity and the availability of drugs that are less cardiotoxic. Metastatic breast cancer

typically requires long-term treatment and perhaps sequential use of several different agents; anthracyclines are still a potentially valuable option in these patients.

If the cardiotoxicity of anthracyclines can be reduced or eliminated, for instance with dexrazoxane, then the potential of anthracycline therapy is enhanced significantly. It is the awareness of cardiotoxicity that has caused a gradual shift away from the anthracyclines, particularly now that less cardiotoxic drugs are becoming available.

However, more recent advances only emphasize that the anthracyclines are going to retain an important place in chemotherapy – and that their use may well increase. In particular, combination of anthracyclines with other agents (e.g., taxanes) is becoming common, and has been associated with high response rates (Gianni et al. 1995). The synergistic effects of anthracyclines and drugs like paclitaxel and trastuzumab unfortunately include synergistic effects on the heart also, and so cardiotoxicity is likely to become a bigger issue. Liposomal delivery of anthracyclines is another promising development, but long-term data are needed, both for efficacy and toxicity.

In assessing the importance of cardiotoxicity in anthracycline treatment, the clinician faces two stumbling blocks. The first is the complete lack of standardization for monitoring cardiac performance, making it difficult to compare data between different studies. The term "cardiotoxicity" is itself difficult to define, and the validity of each of the available parameters [e.g., left ventricular ejection fraction (LVEF)] has been questioned at some time. The second problem is the inconsistency in methods of reporting, which has led to large discrepancies between different data sets. Trials that monitor cardiac events for a period of weeks or months inevitably underestimate the true prevalence of such events.

Some retrospective studies suggest only a relatively low risk of congestive heart failure (CHF) in response to a cumulative dose of 400–500 mg/m^2 doxorubicin (Von Hoff et al. 1979). In contrast, prospective studies suggest a much higher incidence [e.g., 27% in the study by Speyer et al. (Speyer et al. 1992)]. Younger patients are subject to high risk, with 25% of patients < 15 years old showing CHF after 450 mg/m^2 doxorubicin and the incidence increasing linearly above 550 mg/m^2 (Von Hoff et al. 1979). Approximately half of all patients receiving ≥1,000 mg/m^2 experience CHF (Von Hoff et al. 1979). Long-term follow-up studies suggest that cardiotoxicity occurs in as many as 71% of patients treated with anthracyclines as children (Steinherz et al. 1991).

While the probability of cardiotoxicity is clearly related to cumulative anthracycline dose, it is important to remember that the cardiac effects of these drugs start from the first dose. Indeed, CHF has been reported after a single 50-mg/m^2 dose of doxorubicin (Von Hoff et al. 1979). At doxorubicin doses of 200–250 mg/m^2, clinical signs of cardiotoxicity may not be clinically manifest, but may be revealed by measurements such as LVEF.

High doses (≥450–500 mg/m^2) are associated with overt clinical signs. For instance, in one trial reported by Swain et al. (Swain et al. 1997a), 41% of patients receiving a cumulative dose of 450 mg/m^2 doxorubicin and no cardioprotection experienced cardiac events. Adverse cardiac events were defined as a decline in LVEF from baseline of ≥10% and below lower limit of normal (LLN), a decline to ≥5% below LLN, a decline of ≥20% from baseline, or the development of CHF.

It is our conclusion that oncologists underestimate the true risk of anthracycline-induced cardiotoxicity, which may in turn lead to dexrazoxane not being used as a cardioprotectant in patients where it would be valuable. The use of dexrazoxane is recommended by both the Cancer Care Ontario Practice Guideline Initiative (CCOPGI; Seymour et al. 1999) and the American Society of Clinical Oncology (ASCO) guidelines for patients receiving ≥300 mg/m^2 doxorubicin. However, the ASCO guidelines as originally published in 1999 (Hensley et al. 1999) gave great emphasis to one of the two trials published by Swain et al. (Swain et al. 1997a), in which tumor response was higher in placebo patients than dexrazoxane patients, even though a parallel trial and four other randomized trials (and also several smaller trials) showed no difference.

Cardioprotection with dexrazoxane

Several clinical trials have demonstrated the cardioprotective effect of dexrazoxane in patients treated with doxorubicin (Speyer et al. 1988, 1992; Ten Bokkel Huinink et al. 1992; Swain et al. 1997a, 1997b), epirubicin (Venturini et al. 1996; Lopez et al. 1998), or doxorubicin in combination with paclitaxel (Sparano et al. 1999). In the US study of 150 advanced breast cancer patients reported by Speyer et al. (Speyer et al. 1992), 50% of control patients [receiving fluorouracil/doxorubicin/cyclophosphamide (FDC) every 3 weeks] withdrew because of cardiotoxicity, compared with only 8% of those receiving FDC with concomitant dexrazoxane. Of the patients receiving dexrazoxane, 14 reached >1,000 mg/m^2 doxorubicin with no cardiac damage, but no control patients reached this dose.

In the two randomized, double-blind studies described by Swain et al. (Swain et al. 1997a), advanced metastatic breast cancer patients received either FDC plus placebo or FDC plus dexrazoxane. CHF was defined as involving at least two of the following: cardiomegaly, basilar rales, S$_3$ gallop, paroxysmal nocturnal dyspnea, orthopnea, or significant dyspnea on exertion. CHF occurred in 8% of placebo patients but in only 1% of dexrazoxane patients (P <0.001). Cardiac events (defined as above) occurred in 31% of the placebo patients ($n = 285$) but in only 14% of the dexrazoxane patients ($n = 249$). The cardioprotective effects of dexrazoxane were so marked that the study protocols were amended to allow all patients to receive dexrazoxane after 6 cycles of doxorubicin, even before the drug was

approved by the Food and Drug Administration (FDA; Swain et al. 1997a).

Similar results were reported in advanced breast cancer patients receiving a fluorouracil/epirubicin/cyclophosphamide (FEC) protocol (Venturini et al. 1996). Cardiotoxicity (decrease in LVEF to ≤ 45%, or decrease in LVEF from baseline of ≥20 units, or clinical signs of CHF) occurred in 23% of the control patients ($n = 78$), but in only 7% of patients receiving dexrazoxane ($n = 82$; $P = 0.006$). In another randomized trial of high dose epirubicin (160 mg/m^2 every 3 weeks) in breast cancer and soft tissue sarcomas, the incidence of cardiotoxicity was significantly ($P = 0.01$) higher in the control arm (24%) than in the "protected" arm (7%) (Lopez et al. 1998).

Occasional cases of neutropenia or thrombocytopenia have been reported with dexrazoxane. However, bone marrow suppression generally occurs only at doses far in excess of the recommended dose (Vats et al. 1991). Iron overload is common in patients requiring anthracyclines, in some cases due to bone marrow failure. Since dexrazoxane is an iron chelator, there is potentially benefit in these patients (Hershko et al. 1993).

Dexrazoxane and tumor response: a real effect or an anomalous result?

The data from all these trials consistently support the use of dexrazoxane as a cardioprotectant during anthracycline treatment. Analysis of all randomized trials that assessed the possible effects of dexrazoxane on tumor response shows that dexrazoxane did not alter the efficacy of chemotherapy [pooled analysis of five trials and 818 patients (Seymour et al. 1999)]. Why, then, is dexrazoxane used in only 6–7% of European patients undergoing anthracycline treatment?

One possible explanation is the suggestion from a single trial that dexrazoxane may interfere with the antitumor activity of doxorubicin (Swain et al. 1997a). This report detailed two Phase III trials of almost identical design, one of which showed no effect of dexrazoxane on tumor response. In the other trial, objective response rates were 61% and 48% for placebo and dexrazoxane patients, respectively ($P = 0.007$). The tumor response rate in the dexrazoxane group was very similar to what would be expected based on prior studies with doxorubicin. However, the anomaly appears to be in the placebo group, where the response rate (61%) is markedly higher than expected.

This result remains unexplained, and has been heavily relied upon (Schuchter et al. 2002) to suggest that there is a real effect of dexrazoxane on tumor response. It is important to view the result in the context of all the available data, comprising five randomized Phase III studies (as well as numerous smaller trials). In all the other trials there was no effect of dexrazoxane on tumor response, including in the closely related trial also published by Swain et al. (Swain et al. 1997a). As stated above, a meta-analysis of all the available data from the randomized trials ($n = 818$) demonstrates that control/placebo patients have equivalent tumor responses to patients receiving dexrazoxane (Seymour et al. 1999).

Interactions between dexrazoxane and anthracyclines at the cellular level have been thoroughly investigated in a number of breast cancer cell lines (Soudon 1995), but no interference was found. Indeed, such an interference seems implausible when the mechanism of cardioprotection with dexrazoxane (scavenging of free radicals) is in fact unrelated to the cytotoxic mechanism of anthracyclines (topoisomerase II antagonism). Sargent et al. (Sargent et al. 2001) investigated resistance to doxorubicin in a leukemia cell line, and found that development of resistance was markedly decreased in the presence of dexrazoxane.

In the context of an extensive clinical trial program, the effect on response in a single trial may therefore be simply an anomalous result. Certainly, we would expect a real reduction in antitumor efficacy to be reflected in other parameters, especially in overall survival and progression-free survival. In fact, there were no adverse effects on these parameters in the two Swain et al. studies, nor in any of the other studies. According to the FDA, survival time should be regarded as a key endpoint for cancer studies (O'Shaughnessy et al. 1991; FDA 1999).

Optimizing dexrazoxane therapy

Good clinical practice necessitates evaluating which patients should receive a treatment and when they should receive it. In the case of dexrazoxane, prescribing has been inconsistent and has varied between institutions and between countries. The guidelines published by Hensley et al. (Hensley et al. 1999) and revised by Schuchter et al. (Schuchter et al. 2002) focused on only one trial, and have been rigorously rebutted (Hellmann 2000). There is a clear need for extra guidance for the oncologist, and the expert panel reached the following broad conclusions.

Although most of the clinical studies with dexrazoxane have been in patients with breast cancer, there is no reason to suppose that the cardioprotective action of dexrazoxane should be any different in patients with other tumor types. The mechanism of protection is dependent on the cardiotoxic drug (anthracycline) rather than on the neoplastic disease. Therefore, patients with a wide range of tumor types would be expected to benefit from dexrazoxane. Efficacy has already been demonstrated in patients with small-cell lung cancer (Feldmann et al. 1992), Ewing's-type sarcomas (Wexler et al. 1996), and soft tissue sarcomas (Lopez et al. 1998).

Many breast cancer patients will only receive 3–4 cycles of anthracycline treatment. Those patients who are responding to treatment or who have stable disease are the ones most likely to benefit from higher cumulative doses, and therefore they will derive the greatest

benefit from dexrazoxane. It is important to identify these patients, and to treat them with dexrazoxane from the early anthracycline doses onwards. According to the ASCO (Schuchter et al. 2002) and CCOPGI guidelines (Seymour et al. 1999), dexrazoxane use is recommended from a 300-mg/m^2 cumulative doxorubicin dose onwards. This panel believes that dexrazoxane should be used from 150–300 mg/m^2 cumulative doxorubicin onwards, due to the cardiac changes that can already occur at relatively low doses. For epirubicin treatment, dexrazoxane is recommended from the first dose onwards if the cumulative dose is expected to exceed 480 mg/m^2 (Lopez & Vici 1998). Future prospects for identifying those patients most likely to benefit will doubtless involve the use of biomarkers.

Given that the cardiotoxic effects of anthracyclines may only be apparent after a period of months or even years, it is understandable that cardiologists tend to be more insistent on protectant therapy than oncologists who may be treating a patient for a relatively short time. The opinion of the cardiologists in this panel is that dexrazoxane should be used from the very first dose of anthracycline, reflecting the measurable changes in cardiac performance that take place after a single dose.

A pharmacoeconomic analysis in 1997 (Bates et al. 1997) suggested that dexrazoxane treatment in the US costs $5,662 for each cardiac event prevented – a small sum in comparison with the total cost of treating breast cancer. Thus, pharmacoeconomic data support the use of dexrazoxane in patients receiving anthracyclines.

Pediatric use

Cardiotoxicity of anthracyclines is a particular concern in pediatric cancer patients, and the cardiac effects have been well studied and more clearly defined than in adults. Survival times are much longer in this group, and oncologists can usually aim for complete cure. It is therefore worrisome that children seem to be more susceptible to anthracycline-induced cardiotoxicity than adults (Gilladoga et al. 1975; Pratt et al. 1978). Additionally, cardiac problems are likely to affect quality of life more markedly in this younger patient group.

Because of these extra concerns, the pediatric oncologist prescribing anthracyclines should aim for zero cardiotoxicity. This makes it a high priority to assess the benefits of dexrazoxane use in children, as has already been stressed by the French health authority (AFSSaPS 2002). Furthermore, the European Commission has recently recommended that medicines used in adults should be appropriately tested in children where there is a clear need (European Commission 2002).

There is persuasive evidence that dexrazoxane substantially reduces cardiotoxicity in pediatric patients. For instance, Wexler et al. (Wexler et al. 1996) reported 67% subclinical cardiotoxicity in control pediatric patients treated with doxorubicin, but only 22% in patients treated with doxorubicin and dexrazoxane. Pediatric studies with dexrazoxane have included patients with Ewing's sarcoma or related diseases (Wexler et al. 1996), leukemia (Lipshultz et al. 2002), osteosarcoma (Rubio et al. 1995), and various mixed groups such as hepatoblastoma, Wilms tumor, non-Hodgkin lymphoma, and neuroblastoma (Bu'Lock et al. 1993; Schiavetti et al. 1997).

Preliminary data from pediatric trials now in progress suggest very encouraging results with dexrazoxane. For example, cardiotoxicity was assessed in 211 children with acute lymphoblastic leukemia randomized to receive either doxorubicin or doxorubicin with dexrazoxane. The cumulative dose of doxorubicin was up to 300 mg/m^2, and serum troponin-T was used as a marker for cardiac injury. Serum troponin-T was elevated in 45% of the children receiving doxorubicin alone, but in only 23% of those receiving concomitant dexrazoxane ($P < 0.01$; Lipshultz et al. 2002). Preliminary data from recently completed and ongoing trials in pediatric patients with Hodgkin's disease and osteosarcoma appear to confirm that dexrazoxane is highly cardioprotective.

There have been no effects on tumor response in any of the pediatric studies of dexrazoxane. In the randomized study by Lipshultz et al. (Lipshultz et al. 2002), for instance, complete remission was achieved in 85% of doxorubicin patients and 84% of doxorubicin/dexrazoxane patients, after median follow-up of 2.3 years. In the Hodgkin's disease and osteosarcoma trials mentioned above, there have been no obvious effects on antitumor efficacy.

For trials in which children are treated with anthracyclines and dexrazoxane, it is important that survival data be extended over many years, because in some patients the effects of cardiotoxicity may be clinically manifest only after 10 years. It will be very interesting to examine long-term survival data from the trials currently in progress.

Future clinical development

There are several interesting possibilities for future development of dexrazoxane, some of which are already under investigation. Clearly there is enormous potential for the drug in different patient groups, different disease states, and in preventing cardiotoxicity not associated with anthracyclines.

Data on dexrazoxane's protectant effect in elderly patients receiving anthracyclines would be particularly valuable. Elderly patients would typically be excluded from anthracycline treatment, or would receive lower doses, because of their additional cardiac risk. However, anthracyclines would potentially be very useful antitumor agents in these patients if the cardiotoxicity was significantly reduced.

A study on dexrazoxane in adult lymphoma patients would be valuable, since in the case of relapse there is generally no other choice than an anthracycline regimen. High-grade sarcomas in adults are more common than is

generally realized, and the efficacy of adjuvant doxorubicin is dose-related (Brennan et al. 2001). A study of dexrazoxane in these patients would therefore be useful, especially if high doxorubicin doses were used.

There is a potential for dexrazoxane to increase the cumulative dose of anthracycline that can safely be administered, which may be of therapeutic benefit. This has already been noted in some studies; for instance, Swain et al. (Swain et al. 1997b) found that 26% of dexrazoxane patients tolerated cumulative doses ≥ 750 mg/m^2, compared with only 5% of placebo patients.

Anthracyclines probably cause cardiac damage over a period of several days following injection. Dexrazoxane is administered by an intravenous infusion lasting only 15 min, 30 min prior to anthracycline administration, and the elimination half-life is comparatively short [140 min for the deep tissue compartment (Earhart et al. 1982)]. Therefore, there may be further benefit in continuing to administer dexrazoxane over the period of days following each anthracycline dose. A pilot study (Tetef et al. 2001) has demonstrated the feasibility of this approach, and further research will determine whether cardioprotection can be enhanced in this way.

Other indications for dexrazoxane

Dexrazoxane's mechanism of action is through chelation of iron in the Fe^{3+}-(anthracycline)$_3$ complex, thus preventing free radical formation (Hasinoff 1989). Many cardiomyopathies are due to free radical damage. However, the mechanism may not be as clear-cut as was originally supposed, and there may be a more general effect of dexrazoxane on free radical production. For instance, there is already evidence of a reno-protective effect in rats receiving doxorubicin (Herman et al. 1988, 2000) or epirubicin (Dardir et al. 1989), suggesting activity in other tissues.

Dexrazoxane may be cardioprotective in patients receiving chemotherapy other than anthracyclines. There is already anecdotal evidence that dexrazoxane is of value for treating acute cardiac failure and myocardial injury caused by accidental cyclophosphamide overdose (Simbre et al. 2001). A co-operative group trial in patients with locally advanced breast cancer by the Cancer and Leukemia Group B (CALGB) is underway, to study the action of dexrazoxane in complex neoadjuvant regimens which imitate modern clinical practice (CALGB-49808). Future studies of combination therapies are crucial, as these combinations become routine. Trastuzumab may be particularly interesting, since it significantly increases survival in combination with an anthracycline, but at the expense of a high incidence of cardiotoxicity (Slamon et al. 2001). Interactions between antitumor drugs may not be predictable, and so combinations such as doxorubicin/trastuzumab and doxorubicin/paclitaxel all deserve study. The value of dexrazoxane in doxorubicin/paclitaxel treatment has already been confirmed (Gianni et al. 1995; Dombernowsky et al. 1996). Additionally, possible cytoprotective effects of dexrazoxane in radiotherapy need to be investigated.

Work in a cell line (Sargent et al. 2001) has suggested that dexrazoxane may protect against multi-drug resistance. Human leukemia K562 cells developed resistance in the presence of doxorubicin in a concentration-dependent manner. However, when dexrazoxane (20 nM) was included in the medium, resistance was not seen in several months ($P < 0.0001$). Further work is required to extend these in vitro findings and to determine their relevance to chemotherapy.

There is a perceived need for cardioprotection during anthracycline use in breast cancer in the adjuvant setting. It would be interesting to see a definitive study of dexrazoxane in patients undergoing adjuvant treatment.

Conclusions

The panel concludes that anthracyclines continue to be a valuable option in chemotherapy, in spite of their well-documented cardiotoxicity. Recent developments, especially the combinations of anthracyclines with newer agents, ensure that cardiotoxicity is going to be a concern in the future. Although anthracycline-induced cardiotoxicity is dependent on cumulative dose, it actually begins with the first dose.

Dexrazoxane reduces the cardiotoxic effects of anthracyclines, and allows higher anthracycline doses to be used safely (Speyer et al. 1992; Swain et al. 1997b). The weight of evidence shows that dexrazoxane does not affect the antitumor activity of anthracyclines. It is surprising that oncologists have been slow to realize the potential of a drug that reduces or prevents a life-threatening side-effect of chemotherapy. Although more studies are needed to examine the effect of dexrazoxane in a full range of tumor types and in the adjuvant setting, the clinical data available suggest that there is the potential for much more widespread use.

References

Agence Française de Sécurité des Produits de Santé. Besoins en Médicaments Pédiatriques (March 2002) Working report

Bates M, Lieu D, Zagari M, Spiers A, Williamson T (1997) A pharmacoeconomic evaluation of the use of dexrazoxane in preventing anthracycline-induced cardiotoxicity in patients with stage IIIB or IV metastatic breast cancer. Clin Ther 19:167–184

Brennan MF, Alektiar KM, Maki RG (2001) Sarcomas of the soft tissue and bone. Section 1: Soft tissue sarcoma. In: DeVita VT, Hellman S, Rosenberg SA (eds) Cancer: principles and practice of oncology, 6th edn. Lippincott, Williams & Wilkins:1841–1891

Bu'Lock FA, Gabriel HM, Oakhill A, Mott MG, Martin RP (1993) Cardioprotection by ICRF187 against high-dose anthracycline toxicity in children with malignant disease. Br Heart J 70:185–188

Dardir M, Herman EH, Ferrans VJ (1989) Effects of ICRF-187 on the cardiac and renal toxicity of epirubicin in spontaneously hypertensive rats. Cancer Chemother Pharmacol 34:269–275

Dombernowsky P, Gehl J, Boesgaard M, Paaske T, Jensen BV (1996) Doxorubicin and paclitaxel, a highly active combination in the treatment of metastatic breast cancer. Semin Oncol 23:23–27

Earhart RH, Tutsch KD, Koeller JM, Rodriguez R, Robins HI, Vogel CL, Davis HL, Tormey DC (1982) Pharmacokinetics of (+)-1,2-di(3,5-dioxopiperazin-1-yl)propane intravenous infusions in adult cancer patients. Cancer Res 42:5255–5261

European Commission, Enterprise Directorate-General (2002) Better medicines for children. Proposed regulatory actions on paediatric medicinal products. Brussels

Feldmann JE, Jones SE, Weisberg SR, Gandara DR, Lyman GH, York RM, Mailliard JA, Hayes DM, Tranum B, Spaulding MB, Shaikh BS, Khojasteh A, Wajima T, Rivera RR, Abramson N, Horvath WL, Pendergrass KB, Reynolds RD, Gerber M, Winston J, Squillace K, Kline A, Swearengin B, Hess D, Scott D, Banks P, Jones G, Jones D, Gams RA (1992) Advanced small-cell lung cancer treated with CAV (cyclophosphamide + adriamycin + vincristine) chemotherapy and the cardioprotective agent dexrazoxane (ADR-529, ICRF-187, Zinecard). Proc Ann Meet Am Soc Clin Oncol 11:296

Food and Drug Administration (1999) Center for Drug Evaluation and Research. Oncologic Drug Advisory Committee 62nd Meeting

Gianni L, Munzone E, Capri G, Fulfaro F, Tarenzi E, Villani F, Spreafico C, Laffranchi A, Caraceni A, Martini C (1995) Paclitaxel by 3-hour infusion in combination with bolus doxorubicin in women with untreated metastatic breast cancer. High antitumor activity and cardiac effects in a dose-finding and sequence-finding study. J Clin Oncol 13:2688–2699

Gilladoga AC, Manuel C, Tann CC, et al. (1975) Cardiotoxicity of adriamycin (NSC-123127) in children. Cancer Chemother Rep 6:209–214

Hasinoff BB (1989) The interaction of the cardioprotective agent ICRF-187 ((+)-1,2-bis(3,5-dioxopiperazinyl-1-yl)propane), its hydrolysis product (ICRF-198) and other chelating agents with the Fe(III) and Cu(II) complexes of adriamycin. Agents Actions 26:378–385

Hellmann K (2000) Dexrazoxane and the ASCO guidelines for the use of chemotherapy and radiotherapy products: a critique. J Clin Oncol 18:2004–2006

Hensley ML, Schuchter LM, Lindley C, Meropol NJ, Cohen GI, Broder G, Gradishar WJ, Green DM, Langdon RJ Jr, Mitchell RB, Negrin R, Szatrowski TP, Thigpen JT, Von Hoff D, Wasserman TH, Winer EP, Pfister DG (1999) American Society of Clinical Oncology clinical practice guidelines for the use of chemotherapy and radiotherapy protectants. J Clin Oncol 17:3333–3355

Herman EH, el-Hage A, Ferrans VJ (1988) Protective effect of ICRF-187 on doxorubicin-induced cardiac and renal toxicity in spontaneously hypertensive (SHR) and normotensive (WKY) rats. Toxicol Appl Pharmacol 92:42–53

Herman EH, Zhang J, Chadwick DP, Ferrans VJ (2000) Comparison of the protective effects of amifostine and dexrazoxane against the toxicity of doxorubicin in spontaneously hypertensive rats. Cancer Chemother Pharmacol 45:329–334

Hershko C, Link G, Tzahor M, Pinson A (1993) The role of iron and iron chelators in anthracycline cardiotoxicity. Leuk Lymphoma 11:207–214

Krischer JP, Epstein S, Cuthbertson DD, Goorin AM, Epstein ML, Lipshultz SE (1997) Clinical cardiotoxicity following anthracycline treatment for childhood cancer: the pediatric oncology group experience. J Clin Oncol 15:1544–1552

Lipshultz SE, Colan SD, Silverman LB, Levy DE, Dalton VK, Rifai N, Lipsitz SR, Gelber RD, Sallan SE (2002) Dexrazoxane reduces incidence of doxorubicin-associated acute myocardiocyte injury in children with acute lymphoblastic leukemia (ALL). Proc Am Soc Clin Oncol 21:390

Lopez M, Vici P (1998) European trials with dexrazoxane in amelioration of doxorubicin and epirubicin-induced cardiotoxicity. Semin Oncol 25 [Suppl 10]: 55–60

Lopez M, Vici P, Di Lauro L, Conti F, Paoletti G, Ferraironi A, Sciuto R, Giannarelli D, Maini CL (1998) Randomized prospective clinical trial to evaluate cardio-protection of dexrazoxane in patients with advanced breast cancer and soft tissue sarcomas. J Clin Oncol 16:86–92

O'Shaughnessy JA, Wittes RE, Burke G, Friedman MA, Johnson JR, Niederhuber JE, Rothenberg ML, Woodcock J, Chabner BA, Temple R (1991) Commentary concerning demonstration of safety and efficacy of investigational anticancer agents in clinical trials. J Clin Oncol 9:2225–2232

Pratt CB, Ransom JL, Evans WE (1978) Age-related adriamycin cardiotoxicity in children. Cancer Treat Rep 62:1381–1385

Rubio ME, Wiegman A, Naeff MSJ, Voogd PJ, Nooy MA, Cyrus PAH, Voute PA (1995) ICRF 187 (Cardioxane) protection against doxorubicin induced cardiomyopathy in paediatric osteosarcoma patients. Proc Am Soc Clin Oncol 14:440

Sargent JM, Williamson CJ, Yardley C, Taylor CG, Hellmann K (2001) Dexrazoxane significantly impairs the induction of doxorubicin resistance in the human leukaemia line, K562. Br J Cancer 84:959–964

Schiavetti A, Castello MA, Versacci P, Varrasso G, Padula A, Ventriglia F, Werner B, Colloridi V (1997) Use of ICRF-187 for prevention of anthracycline cardiotoxicity in children: preliminary results. Pediatr Hematol Oncol 14:213–222

Schuchter LM, Hensley ML, Meropol NJ, Winer EP (2002) 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 20:2895–2903

Sehested M, Jensen PB (1996). Mapping of DNA topoisomerase II poisons (etoposide, clerocidin) and catalytic inhibitors (aclarubicin, ICRF187) to four distinct steps in the topoisomerase II catalytic cycle. Biochem Pharmacol 51:879–886

Seymour L, Bramwell V, Moran LA (1999) Use of dexrazoxane as a cardioprotectant in patients receiving doxorubicin or epirubicin chemotherapy for the treatment of cancer. Cancer Prev Control 3:145–159 (2002 update available: http://www.cco-pebc.ca/guidelines/sys/full12_5.pdf)

Simbre II VC, Adams MJ, Deshpande SS, Duffy SA, Miller TL, Lipshultz SE (2001) Cardiomyopathy caused by antineoplastic therapies. Curr Treat Opt Cardiovasc Med 3:493–505

Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344:783–792

Soudon J (1995) Study of the in vitro cytotoxicity of doxorubicin combined with Cardioxane® to 9 breast cancer cell lines. French Authorisation Application File for Cardioxane®

Sparano JA, Speyer J, Gradishar WJ, Liebes L, Sridhara R, Mendoza S, Fry D, Egorin MJ (1999) Phase I trial of escalating doses of paclitaxel plus doxorubicin and dexrazoxane in patients with advanced breast cancer. J Clin Oncol 17:880–886

Speyer JL, Green MD, Kramer E, Rey M, Sanger J, Ward C, Dubin N, Ferrans V, Stecy P, Zeleniuch-Jacquotte A, et al (1988) Protective effect of the bispiperazinedione ICRF-187 against doxorubicin-induced cardiac toxicity in women with advanced breast cancer. New Engl J Med 319:745–752

Speyer JL, Green MD, Zeleniuch-Jacotte A, Wernz JC, Rey M, Sanger J, Kramer E, Ferrans V, Hochster H, Meyers M, Blum RH, Feit F, Attubato M, Burrows W, Muggia FM (1992) ICRF-187 permits longer treatment with doxorubicin in women with breast cancer. J Clin Oncol 10:117–127

Steinherz LJ, Steinherz PG, Tan CTC, Heller G, Murphy ML (1991) Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 266:1672–1677

Swain SM, Whaley FS, Gerber MC, Weisberg S, York M, Spicer D, Jones SE, Wadler S, Desai A, Vogel C, Speyer J, Mittelman A, Reddy S, Pendergrass K, Velez-Garcia E, Ewer MS, Bianchine JR, Gams RA (1997a) Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. J Clin Oncol 15:1318–1322

Swain SM, Whaley, FS, Gerber MC, Ewer MS, Bianchine JR, Gams RA (1997b) Delayed administration of dexrazoxane provides cardioprotection for patients with advanced breast cancer treated with doxorubicin-containing therapy. J Clin Oncol 15:1333–1340

Ten Bokkel Huinink WW, Schreuder JE, Dubbelman R, Bierhorst F, van Tinteren H, Dalesio O, Valdés Olmos RA, McVie JG (1992) ICRF 187 protects against doxorubicin induced cardiomyopathy. Ann Oncol 3:114

Tetef ML, Synold TW, Chow W, Leong L, Margolin K, Morgan R, Raschko J, Shibata S, Somlo G, Yen Y, Groshen S, Johnson K, Lenz HJ, Gandara D, Doroshow JH (2001) Phase I trial of 96-hour continuous infusion of dexrazoxane in patients with advanced malignancies. Clin Cancer Res 7:1569–1576

Vats T, Kamen B, Krischer JP (1991) Phase II trial of ICRF-187 in children with solid tumors and acute leukemia. Invest New Drugs 9:333–337

Venturini M, Michelotti A, Del Mastro L, Gallo L, Carnino F, Garrone O, Tibaldi C, Molea N, Bellina RC, Pronzato P, Cyrus P, Vinke J, Testore F, Guelfi M, Lionetto R, Bruzzi P, Conte PF, Rosso R (1996) Multicenter randomized controlled clinical trial to evaluate cardio-protection of dexrazoxane versus no cardio-protection in women receiving epirubicin chemotherapy for advanced breast cancer. J Clin Oncol 14:3112–3120

Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, Muggia FM (1979) Risk factors for doxorubicin induced congestive heart failure. Ann Intern Med 91:710–717

Wexler LH, Andrich MP, Venzon D, Berg SL, Weaver-McClure L, Chen CC, Dilsizian V, Avila N, Jarosinski P, Balis FM, Poplack DG, Horowitz ME (1996) Randomized trial of the cardioprotective agent ICRF-187 in pediatric sarcoma patients treated with doxorubicin. J Clin Oncol 14:362–372