Clinical Status and Optimal Use of the Cardioprotectant, Dexrazoxane

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There are many challenges facing those involved in chemotherapy drug development. In addition to identification of new agents, clinical investigators must address questions regarding the optimal methods of administration of established agents so as to maximize efficacy and minimize toxicity. Treatment toxicity affects not only morbidity and mortality but also issues of dose intensity, quality of life, and health-care costs. Therefore, there is great interest in preventing the side effects associated with chemotherapy.

There are two approaches to toxicity prevention, and both have been successful. The first involves early rescue after chemotherapy exposure, as in the use of the myeloid growth factors granulocyte-colony stimulating factor (G-CSF [Neupogen]) and granulocyte-macrophage colony-stimulating factor (GM-CSF [Leukin, Prokine]). The second approach prevents normal tissue injury through pretreatment with a chemoprotectant, such as amifostine (Ethyol), mesna (Mesnex), and dexrazoxane (Zinecard).

Dr. Blum provides a comprehensive review of anthracycline-associated cardiac toxicity and the clinical development of the cardioprotectant drug dexrazoxane. Based on the results of three prospectively randomized, placebo-controlled clinical trials,[1-3] dexrazoxane was approved for use in the US in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m² and who would benefit from continued doxorubicin therapy.

An Ideal Chemoprotectant?
To put dexrazoxane into perspective, we may ask how well it fulfills four characteristics of an “ideal” chemoprotectant:

1. Is it nontoxic at effective doses?
2. Does it have a simple schedule of administration?
3. Does it selectively protect normal target tissue but not cancer cells?
4. Does it provide complete protection against the specific toxicity?

In terms of toxicity related to dexrazoxane, the randomized studies reported by Speyer et al and Swain et al[1-3] demonstrate that it is well-tolerated when used with the combination of fluorouracil, doxorubicin, and cyclophosphamide (FDC). The only toxicities referable to dexrazoxane were pain at the injection site and modest increases in neutropenia and thrombocytopenia that were of little clinical significance. The pharmacology of dexrazoxane allows for a simple and convenient dosing schedule.

Dexrazoxane shows target organ specificity that is not absolute, however. Cardiac toxicity from anthracyclines is postulated to be an iron-dependent process, with cardiac tissue susceptibility related to its lower levels of superoxide dismutase and catalase. Dexrazoxane metabolites have iron-chelating ability, and preclinical models suggest more efficient uptake and metabolism by myocytes than by cancer cells. The largest of the three randomized clinical trials showed a decreased response rate (48% vs 63%, P = .007) in the group receiving dexrazoxane, but there was...
no difference in time to progression or survival.[2] This finding of an adverse effect on tumor response, although by no means conclusive, serves as a cautionary note and should not be discounted. It has led to the FDA recommendation that dexrazoxane be used only after a cumulative doxorubicin dose of 300 mg/m² has been reached, and indicates the need for further clinical trials.

The Question of End Points

As Dr. Blum indicates, dexrazoxane successfully reduces the risk of cardiotoxicity as measured by nuclear imaging, endomyocardial biopsy, and development of clinical congestive heart failure. These clinical end points validate the preclinical findings. While such end points as dose of doxorubicin delivered and changes in ejection fraction may serve as proof of principle, the most clinically relevant end points are patient survival, symptoms, and quality of life. It is in these areas that chemoprotectants in general face the greatest challenge. Future studies should focus on end points that are most relevant to clinicians and patients. Long-term follow-up of patients with cured malignancies treated with dexrazoxane will determine whether early subclinical benefits in cardiac function result in improved long-term, clinically meaningful outcomes.

Dexrazoxane is well-tolerated and easily administered, shows relative cardiac specificity, and reduces the risk of cardiac toxicity in women with breast cancer who are treated with FDC. Dr. Blum suggests that one may extrapolate the results of studies conducted in breast cancer to other disease settings. Additional randomized trials will determine dexrazoxane’s effectiveness as a cardioprotectant and its impact on tumor response in other disease sites and age groups, with other doxorubicin-based regimens, and with other cardiotoxic drugs. More data are also needed regarding its safety (effect on tumor progression) when administered at the initiation of anthracycline therapy, especially in patients with curable malignancies for whom long-term outcome is of particular interest. We believe that until such results are available from these studies, caution should be exercised in the ad hoc use of dexrazoxane.

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