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Current Approaches in Cytoprotection: the Role of Amifostine (Ethyol®) in Altering and Ameliorating Toxicities in Cancer Therapy

R.M. Bukowski

Experimental Therapeutics Program, The Cleveland Clinic Foundation, Department of Hematology/Oncology, Cleveland Clinic Cancer Center/T40, 9500 Euclid Avenue, Cleveland, Ohio 44195-5237, U.S.A.

RECENT DEVELOPMENTS in supportive care for patients receiving cancer chemotherapy have focused on attempts to decrease the toxicity of chemotherapeutic agents without affecting the antitumour efficacy of these treatment programmes. An area of intense interest and clinical research has been the co-administration of growth factors to accelerate haematopoietic recovery. Clearly, this has met with success, with some patients experiencing amelioration of morbidity secondary to myelosuppression.

Coincidental with these developments, the concept of cytoprotection has evolved. The basis of this approach involves selective protection of normal tissues from the toxicity of antineoplastic therapy, without impairing the cytotoxic properties of that therapy. Examples now being utilised at The Cleveland Clinic Foundation involve regional cytoprotection, with regimens such as oral cryotherapy and regional administration of sodium thiosulphate during intraperitoneal cisplatin therapy. However, the development of systemic agents to decrease toxicity has been difficult. Problems encountered have included a decrease in the antitumour efficacy of the chemotherapy administered and/or excessive toxicity of various cytoprotective agents.

The international congress *Ethyol®: Current and Future Applications in Cytoprotection* focused on the drug amifostine (Ethyol®, WR-2721), a prodrug that forms an activated free thiol, WR-1065, when dephosphorylated by alkaline phosphatase. This metabolite appears to be somewhat selective in its entry into nonmalignant cells and, therefore, may protect against toxicity associated with alkylating agents and platinum-containing regimens. The congress reviewed the preclinical data supporting amifostine's role as a cytoprotective agent and also the clinical studies leading to the approval of this agent for use in patients receiving cyclophosphamide and cisplatin for ovarian carcinoma.

Papers presented herein provide the preclinical and biochemical basis for amifostine and its effects on a broad range of cell types, including both neoplastic and non-neoplastic cell lines. The pharmacokinetic and pharmacodynamic effects in animal models and humans are outlined by Drs van der Vijgh and Korst and provide a rationale for the administration schedules utilised.

The potential role of amifostine in patients with both haematological and nonhaematological malignancies is also explored. Its role in the protection of bone marrow purged *ex vivo* with agents such as maphosfamide, and a comparison of the effects of amifostine on normal haematopoietic cells and leukaemia cells during purging, are discussed by Douay and coworkers. It appears that amifostine can indeed protect normal $CD34^+$ haematopoietic stem cells and most interestingly, may actually enhance selective killing of leukaemia cells during *ex vivo* purging. Clinical results in these areas, however, remain preliminary.

The use of amifostine in patients with solid tumours is another major area of interest, and the data in ovarian cancer patients receiving a variety of standard anticancer drugs clearly demonstrate its cytoprotective effects. These data include reduced myelosuppression and nephrotoxicity. In a randomised phase II study, Dr Budd and coworkers report that amifostine may also decrease the myelosuppressive toxicity of carboplatin, resulting in less thrombocytopenia. The effects of this drug in patients receiving radiotherapy are also of interest and, indeed, were an initial application.

The purpose of this supplement is to review some of the basic scientific knowledge concerning cytoprotection with a focus on the biochemical basis and preclinical data supporting amifostine's use in this setting. Amifostine's clinical role is now developing, and clearly it possesses significant clinical effects that alter and ameliorate certain toxicities associated with cisplatin and alkylating agent therapy. Exploration of additional schedules, other indications and different settings will expand our knowledge and database concerning the effects of this drug, especially in such areas as its potentiation of the antineoplastic effects of certain agents.