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The Need for Cytoprotection

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The toxicity associated with chemotherapy is significant and dose limiting. Multiple organ systems can be affected, with both acute and chronic side effects producing adverse effects. The concept of cytoprotection, or the selective protection of normal tissues is a strategy now being investigated in preclinical and clinical models. Systemic approaches have included the use of compounds such as sodium thiosulphate, diethyldithiocarbamate and amifostine. The most promising results have been obtained with the organic thiophosphate compound amifostine (Ethyol®, WR-2721). Copyright © 1996 Elsevier Science Ltd

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THE TOXICITY associated with chemotherapeutic agents used in the systemic therapy of malignancy can be significant and ultimately can limit the ability to deliver effective therapy. A broad range of organ systems may be adversely affected, with dose-limiting toxicity occurring in the bone marrow, gastrointestinal tract, kidney, bladder, lung and nervous and cardiovascular systems. Because dose intensity [1] may be related to clinical outcome measures, such as disease-free and overall survival [2–5], chemotherapy-associated toxicity may affect not only morbidity but also treatment outcome. However, in many patients, maintenance of dose intensity or dose intensification may be limited by such effects. The resulting treatment delays or dose reductions may, therefore, potentially impair the effectiveness of treatment. Because of these factors, investigations designed to decrease side effects or limit the normal tissue toxicity have been a priority in medical oncology during the past 5–10 years. Approaches that reduce the systemic toxicity of chemotherapy without impairing its effectiveness are, therefore, of great interest.

Areas investigated to date include the administration of haematopoietic growth factors to accelerate recovery from myelosuppression [6] and the use of cytoprotective agents to minimise normal tissue injury [7,8]. The studies with colony-stimulating factors such as granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor and erythropoietin [6, 9, 10] demonstrate amelioration of clinical toxicity associated with myelosuppression secondary to chemotherapy. The normal cell population affected by these factors is, in most instances, limited to haematopoietic precursors. Mechanisms of action generally include accelerated recovery, but the possibility that G-CSF [11] or interleukin-11 [12] may confer protection against mucositis is now under investigation. The concept of cytoprotection or selective protection of normal tissues is an alternative approach. This strategy has been investigated in preclinical models [13], but to date clinical applications have been limited.

The mechanisms by which antitumour agents damage or kill tumour and normal cells are still poorly understood. They may include the effects of reactive species such as organoplatinum compounds [14] or generation of oxygen free radicals by agents such as the anthracyclines [15]. Attempts to develop cytoprotective strategies have, therefore, been largely empiric; but clearly progress has been made in certain areas [16]. The goals of selective cytoprotection include the prevention of multiorgan toxicity without affecting the antitumour activity of chemotherapy [17]. The normal cells are protected selectively, and both acute and chronic toxicity may be decreased [18].

One approach employing regional cytoprotection, utilising oral cryotherapy to decrease or prevent mucositis associated with 5-fluorouracil and leucovorin chemotherapy, has been demonstrated to be effective in a randomised trial [19]. Another regional approach involves the systemic administration of sodium thiosulphate during intraperitoneal therapy with cisplatin [20]. Mensa administration with ifosfamide to prevent urinary tract epithelial cell injury by the metabolite acrolein [21] is a third example by which cytoprotective effects are limited to a specific anatomical compartment.

Systemic approaches with selective protection of normal cells from the toxic effects of chemotherapy have also been investigated [22]. Various agents have been tested for their cytoprotective effects when administered with systemic chemotherapy (Table 1). These include the compound sodium thiosulphate, diethyldithiocarbamate and amifostine. Sodium thiosulphate has been studied for its ability to decrease the toxicity of high-dose cisplatin [20]. This compound directly inactivates cisplatin [23] and the possibility, therefore, of decreased antitumour effects with systemic administration is a concern. A second drug, diethyldithiocarbamate, has decreased cisplatin

Table 1. Systemic chemoprotective agents

Dexrazoxane (zinecard®, ICRF 187)
Amifostine (ethyol®, WR-2721)
Sodium thiosulphate
Diethyldithiocarbamate (imuthiol®)

Table 2. Amifostine: potential future investigations

- Use with other regimens:
  Anthracyclines
  Paclitaxel/cisplatin
  Paclitaxel/carboplatin
- Use with various haemotopoietic growth factors
- Use as part of dose-intense regimens
- Use with combined-modality regimens
- Use in transplant setting:
  Autologous bone marrow transplantation
  Ex vivo purging
- Impact on quality of life and costs of therapy

toxicity in both preclinical models and clinical trials employing cisplatin-based regimens [24]. Unfortunately, secondary neurological toxicity and a reduction in antitumour activity have been noted [25].

The most promising results to date have been obtained with the organic thiophosphate compound amifostine (Ethyol®, WR-2721, Schering-Plough International, Kenilworth, New Jersey, U.S.A.). This agent (Figure 1) is a prodrug that is relatively nonreactive with electrophilic groups of chemotherapeutic agents. When amifostine is dephosphorylated by alkaline phosphatase, an activated free thiol (WR-1065) is formed. This metabolite appears to enter nonmalignant cells selectively [16] by facilitated diffusion, and potentially provides protection against oxygen-based radicals and electrophilic reactive drugs, such as alkylating agents and platinum-containing drugs.

Initially, this compound was developed during extensive screening of sulphydryl-containing compounds, following the demonstration that cysteine provided *in vivo* protection against radiation-induced injury. Preclinical studies with amifostine [13] clearly indicated it could increase the radioresistance of normal tissues and decrease the systemic toxicity of alkylating agents and cisplatin. It was then studied in a series of phase I, II and III clinical trials, and its cytoprotectant effects and toxicity profile were clarified [18, 26, 27]. Based on the ability of amifostine to decrease the myelosuppressive effects of cyclophosphamide and chronic renal toxicity produced by repeated cisplatin administration, this agent is now approved in several European countries as a cytoprotectant.

Areas in which future investigations of amifostine may be of interest are illustrated in Table 2. These include the combination of amifostine and haematopoeitic growth factors, the effects on toxicity of anthracycline- or paclitaxel-containing regimens and the role of amifostine in patients receiving dose-intense regimens, combined modality approaches or bone marrow/peripheral blood stem cell transplants. Also, the effect of this agent on quality of life and costs of therapy should be investigated to develop models to demonstrate its overall benefit as a clinical cytoprotectant.

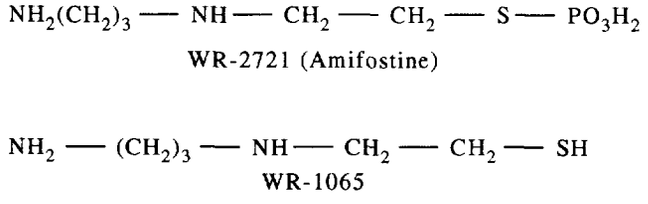

Figure 1. Structure of amifostine (WR-2721) and its prodrug WR-1065.

1. Hryniuk WM, Figuerdo A, Goodyear M. Applications of dose intensity to problems in chemotherapy of breast and colorectal cancer. *Semin Oncol* 1987, **14** (Supplement 4), 3–11.
2. Wood WC, Budman DR, Korzun AH, *et al.* Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. *N Engl J Med* 1994, **330**, 1253–1259.
3. Dana BW, Dahlberg S, Miller TP, *et al.* m-MACOD treatment for intermediate- and high-grade malignant lymphomas: a Southwest Oncology Group phase II trial. *J Clin Oncol* 1990, **8**, 1155–1162.
4. Mayer RJ, Davis RB, Schiffer CA, *et al.* Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. *N Engl J Med* 1994, **331**, 896–903.
5. Linch DC, Winfield D, Goldstone AH, *et al.* Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomized trial. *Lancet* 1993, **341**, 1051–1054.
6. Crawford J, Ozer H, Stoller R, *et al.* Reduction by granulocyte colony-stimulating factor of fever and neutropenia by chemotherapy in patients with small-cell lung cancer. *N Engl J Med* 1991, **325**, 164–170.
7. Glover D, Glick JH, Weiler C, Hurowitz S, Kligerman MM. WR-2721 protects against the hematologic toxicity of cyclophosphamide: a controlled phase II trial. *J Clin Oncol* 1986, **4**, 584–588.
8. Betticher DC, Anderson H, Ranson M, Meely K, Oster W, Thatcher N. Carboplatin combined with amifostine, a bone marrow protectant, in the treatment of non-small-cell lung cancer: a randomized phase II study. *Br J Cancer* 1995, **72**, 1551–1555.
9. Vadhan-Raj S, Broxmeyer HE, Hittleman WN, *et al.* Abrogating chemotherapy-induced myelosuppression by recombinant granulocyte-macrophage colony-stimulating factor in patients with sarcoma: protection at the progenitor cell level. *J Clin Oncol* 1992, **10**, 1266–1277.
10. Case DC Jr, Bukowski RM, Carey RW, *et al.* Recombinant human erythropoietin therapy for anemic cancer patients on combination chemotherapy. *J Natl Cancer Inst* 1993, **85**, 801–806.
11. Gabrilove JL, Jakubowski A, Scher H, *et al.* Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. *N Engl J Med* 1988, **318**, 1414–1422.
12. Keith JC, Albert L, Sonis ST, Pfeiffer CJ, Schaub RB. IL-11 — a pleiotropic cytokine: exciting new effects of IL-11 on gastrointestinal mucosal biology. In Murphy MJ, ed. *Polyfunctionality of Hematopoietic Regulators*. Dayton, OH, AlphaMed Press, 1994, 79–90.
13. Yuhas JM, Spellman JM, Jordan SW, *et al.* Treatment of tumors with the combination of WR-2721 and cis-dichlorodiammineplatinum (II) or cyclophosphamide. *Br J Cancer* 1980, **42**, 574–585.
14. Reed E, Ozols RF, Tarone R, *et al.* Platinum–DNA adducts in leukocyte DNA correlate with disease response in ovarian cancer patients receiving platnium-based chemotherapy. *Proc Natl Acad Sci USA* 1987, **84**, 5024–5028.
15. Myers CE. Anthrocyclines. In Chabner B, ed. *Pharmacologic Principles of Cancer Treatment*. Philadelphia, WB Saunders, 1982, 416–434.
16. Capizzi RL, Scheffler BJ, Schein PS. Amifostine-mediated protection of normal bone marrow from cytotoxic chemotherapy. *Cancer* 1993, 72 (Supplement 11), 3495-3501.
17. Schuchter LM, Luginbuhl WE, Meropol NJ. The current status of toxicity protectants in cancer therapy. *Semin Oncol* 1992, **19**, 742–751.
18. Kemp G, Rose P, Lurain J, *et al.* Amifostine pretreatment for protection against cyclophosphamide- and cisplatin-induced toxicities: results of a randomized control trial in patients with advanced ovarian cancer. *J Clin Oncol* 1996, **14**, 2101–2112.
19. Mahood DJ, Dose AM, Loprinzi CL, *et al.* Inhibition of fluorouracil-induced stomatitis by oral cryotherapy. *J Clin Oncol*

1991, **9**, 449–452.
20. Howell SB, Pfeifle CE, Wung WE, Olshen RA. Intraperitoneal *cis*-diamminedichloroplatinum with systemic thiosulfate protection. *Cancer Res* 1983, 43, 1426–1431.
21. Cox P. Cyclophosphamide cystitis: identification of acrolein as the causative agent. *Biochemi Pharmacol* 1979, **28**, 2045–2049.
22. Lewis C. A review of the use of chemoprotectants in cancer chemotherapy. *Drug Safety* 1994, **11**, 153–162.
23. Cisplatin. In Dorr RT, von Hoff DD, eds, *Cancer Chemotherapy Handbook*. East Norwalk, Conn, Appleton and Lange, 1994, 286–298.
24. Berry JM, Jacobs C, Sikic B, Halsey J, Borch RF. Modification of cisplatin toxicity with diethyldithiocarbamate. *J Clin Oncol* 1990, **8**, 1585–1590.
25. Qazi R, Chang AY, Borch RF, *et al.* Phase I clinical and pharmacokinetic study of diethyldithiocarbamate as a chemoprotector from toxic effects of cisplatin. *J Natl Cancer Inst* 1988, **80**, 1486–1488.
26. Budd GT, Ganapathi R, Bauer L, *et al.* Phase I study of WR-2721 and carboplatin. *Eur J Cancer* 1993, **29A**, 1122–1127.
27. Budd GT, Bukowski RM, Adelstein D, *et al.* Mature results of a randomized trial of carboplatin and amifostine versus carboplatin alone in patients with advanced malignancies. *Proc Am Soc Clin Oncol* 1996, **15**, 532 (Abstract).