1. Marty M, Pouillart P, Scholl S, *et al.* Comparison of the 5-hydroxytryptamine (serotonin) antagonist ondansetron (GR 38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 1990, **322**, 816–821.
2. Roila F, Tonato M, Cognetti F, *et al.* Prevention of cisplatin-induced emesis: a double-blind multicentre randomized cross-over study comparing ondansetron and ondansetron plus dexamethasone. *J Clin Oncol* 1991, **9**, 675–678.
3. Borison HL, McCarty LE. Neuropharmacology of chemotherapy induced emesis. *Drugs* 1983, **25**, 8–17.
4. Tyson LB, Clark R, Gralla RJ. High-dose metoclopramide: control of dacarbazine-induced emesis in a preliminary trial. *Cancer Treat Rep* 1982, **66**, 2108.
5. Basurto C, Roila F, Tonato M, *et al.* Antiemetic activity of high-dose metoclopramide combined with methylprednisolone versus metoclopramide alone in dacarbazine-treated cancer patients. *Am J Clin Oncol* 1989, **12**(3), 235–238.
6. Tixi L, Bolli E, Guglielmi A, *et al.* Dacarbazine and fotemustine in advanced colorectal cancer. *Eur J Cancer* 1993, **29**, 476.

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A Randomised Double-blind Placebo Controlled Clinical Trial Assessing the Tolerability and Efficacy of Glutathione as an Adjuvant to Escalating Doses of Cisplatin in the Treatment of Advanced Ovarian Cancer

F.X. Parnis, R.E. Coleman, P.G. Harper, D. Pickering, C. Topham, J.R. Whittington and M. Tedeschi

CISPLATIN IS a most active drug in the treatment of epithelial ovarian cancer. The efficacy of this drug is dose dependent, as shown in a recent randomised study of two doses of cisplatin given with a fixed dose of cyclophosphamide [1]. This trial was closed early when an interim analysis indicated a highly significant survival advantage for those treated with the higher dose (100 mg/m^2) of cisplatin. The toxic effects of the treatment were also significantly greater in the high dose arm, and the authors identified the need to alleviate cisplatin toxicities.

Glutathione is a naturally occurring thiol tripeptide with a high affinity for heavy metals, and potentially able to reduce cisplatin toxicities. In non-randomised studies, glutathione has enabled high doses of cisplatin to be administered with only modest toxicity and without compromising its cytotoxic activity [2]. When used in animal models, glutathione has diminished cisplatin neurotoxicity [3].

We performed a randomised, double-blind, placebo controlled study in patients with advanced ovarian cancer to assess the efficacy of glutathione as an adjunct to escalating doses of cisplatin. Three groups, each of 12 cisplatin-treated patients (6 glutathione and 6 placebo), were treated. The daily dose of cisplatin was fixed at 40 mg/m^2 and given over 2 h. In Group 1, this treatment was for 2 successive days, Group 2 for 3 days and Group 3 for 4 days, repeated every 4 weeks. The glutathione-treated patients were treated with a fixed dose of glutathione (1.5 g/m^2) given by infusion over 15 min prior to each cisplatin treatment. A total of 14 patients were treated in Group 1 (2 replacements for protocol violators). Recruitment to the trial was stopped after 8 patients (5 active and 3 placebo) had entered Group 2. Ototoxicity had proved more common than expected, and 4 patients in this group were withdrawn because of grade II toxicity encountered. No patients were entered in Group 3.

Clinical assessments, laboratory tests, and neurological and audiological examinations were performed on all treated patients, but no significant differences were noted between the active and placebo groups. Ototoxicity was noted in both glutathione- and placebo-treated patients. Independent assessment of the audiograms suggested less toxicity in the glutathione-treated patients. We feel glutathione failed to significantly protect against cisplatin toxicity because cisplatin was administered over 2 h. Glutathione has a short half-life, and it has recently been shown that 30 min cisplatin infusions are optimal when combined with glutathione [4]. Further randomised clinical studies with these two drugs using optimal drug scheduling are clearly needed.

Correspondence to F.X. Parnis at the Department of Medical Oncology, Royal Adelaide Hospital, Adelaide, South Australia, SA 5000, Australia. P.G. Harper is at the Department of Medical Oncology, Guy's Hospital, London SE1 9RT, U.K.; R.E. Coleman is at the Department of 'Oncology', Weston Park Hospital, Sheffield S10 2SJ, U.K.; D. Pickering is at the Department of Clinical Oncology, Penbury Hospital, Kent TW2 4QJ, U.K.; C. Topham is at the Department of Clinical Oncology, St Luke's Hospital, Guildford, U.K.; J.R. Whittington is at the Department of Statistics, Twyford, Buckingham MK18 4EL, U.K.; and M. Tedeschi is at Boehringer Mannheim, Italia SpA 1-20052, Monza, Italy.
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1. Kaye SB, Lewis CR, Paul J, *et al.* Randomised study of two doses of cisplatin with cyclophosphamide in epithelial ovarian cancer. *Lancet* 1992, **340**(8815), 329–333.
2. Di Re F, Bohm S, Oriana S, *et al.* High dose cisplatin and cyclophosphamide with glutathione in the treatment of advanced ovarian cancer. *Ann Oncol* 1993, **4**(1), 55–61.
3. Hamers FP, Brakkee JH, Cavaletti E, *et al.* Reduced glutathione protects against cisplatin-induced neurotoxicity in rats. *Cancer Res* 1993, **53**(3), 544–549.
4. Pirovano C. Peripheral neurotoxicity following high dose cisplatin with glutathione: clinical and neurophysiological assessment. *Tumori* 1992, **78**, 253–257.