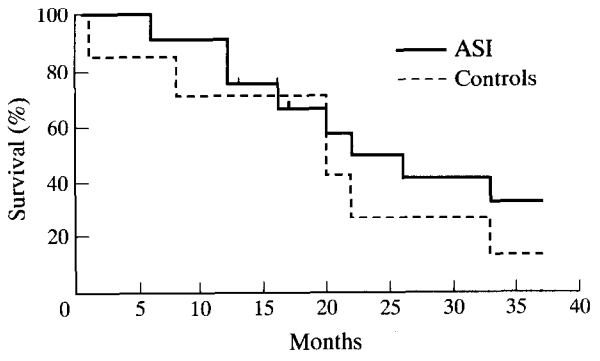

Figure 3. Survival of patients with metastatic renal cell carcinoma (RCC).

was no notable difference in long term survival between both groups (Figure 3).

According to the data presented, patients with locally advanced non-metastatic tumours undergoing ASI after nephrectomy show a tendency towards a lower recurrence rate compared to patients receiving no further treatment after surgery. However, in metastatic disease, there was no notable difference in survival between patients receiving ASI compared with patients receiving other treatment regimes or no palliative treatment at all after tumour nephrectomy. Therefore, tumour nephrectomy combined with ASI alone in patients with metastatic RCC is insufficient and shows no improvement compared to other palliative treatment regimes.

In future, the preparation techniques need to be optimised, and *in vitro* expansion of RCC cells has to be used in order to obtain enough vials for ASI vaccination, even in patients with small or fibrotic and necrotic tumours. The identification of tumour-associated antigens in RCC is one of the major goals for developing more effective adjuvant and palliative treatment regimes. The prolongation of immunostimulation after vaccination might improve the activation, maturation and response of cytotoxic lymphocytes involved in immunological tumour control. For this purpose, new adjuvants are being developed [5]. Non-specific stimulation of the immune system by cytokines, e.g. interferons and interleukins, may be helpful for increasing immunoreactivity in RCC patients undergoing ASI treatment.

1. Goepel M, Rübben H. Adjuvant therapy in renal cancer. *World J Urol* 1991, **9**, 232–236.
2. Schirrmacher V, von Hoegen P, Schlag P, *et al.* Active specific immunotherapy with autologous tumor cell vaccines modified by Newcastle Disease Virus: experimental and clinical studies. In Schirrmacher V, Schwartz-Albiez R, eds. *Cancer Metastasis*. New York, Springer, 1989, 157–170.
3. Hinkel A, de Riese W, Laumann D, Falkenberg FW, Senge T, Hertle L. Active specific immunotherapy with autologous virus modified tumor vaccines in renal cell carcinoma. *J Urol* 1994, **151**(5) (Suppl.), 316A.
4. La Vecchia C, Levi F, Lucchini F, Negri E. Descriptive epidemiology of kidney cancer in Europe. *J Nephrol* 1992, **5**, 37–43.
5. Alving CR, Detrick B, Richards RL, Lewis MG, Shafferman A, Eddy GA. New adjuvant strategies for experimental vaccines. *Ann New York Acad Sci* 1993, **690**, 265–275.

European Journal of Cancer Vol. 31A, No. 10, pp. 1720–1721, 1995.

0959–8049/95 $9.50 + 0.00

0959-8049(95)00313-4

Ondansetron for the Control of Dacarbazine-induced Emesis

E. Campora, S. Chiara and C. Aschele

THE MAJORITY of anti-emetic trials have addressed the problem of emesis induced by cisplatin-containing chemotherapy regimens, and it has been demonstrated that ondansetron provides effective prophylaxis. The addition of dexamethasone to ondansetron further improves anti-emetic control [1, 2]. Even if dacarbazine is a commonly used chemotherapeutic agent with high emetogenic potential [3], very few studies concerning the control of dacarbazine-induced emesis have been reported [4, 5]. The following open study was performed to assess the anti-emetic efficacy of the 5-HT3-receptor antagonist, ondansetron, in patients receiving chemotherapy including dacarbazine.

19, chemotherapy-naive, advanced colorectal cancer patients, median age 64 years, median ECOG performance status 1, entered a phase II clinical trial of dacarbazine 500 mg/m^2 followed after 2 h by the nitrosourea, fotemustine, 100 mg/m^2 day 1, every 4 weeks [6]. At the first course of therapy, 18 patients received ondansetron 8 mg orally 1 h prior to chemotherapy and then after 6 and 12 h. Ondansetron 8 mg orally three times daily was given on days 2 and 3. All patients were treated on an outpatient basis. Emesis was evaluated as follows: complete protection = no emetic episodes; major protection = one–two episodes; minor protection = three–four episodes; no protection ≥five episodes. Nausea was graded as follows: zero = none; one = mild, induced by certain odours or flavours; two = moderate, food intake compromised; three = food intake impeded.

Results of protection from acute emesis (any emetic episode occurring within 24 h of chemotherapy) with ondansetron were: 8 (44.4%) and 7 (38.8%) patients had complete and major emetic protection, respectively. No patient experienced more than five emetic episodes. Nausea was absent in 8 patients (44.4%) or mild in 6 cases (33.3%). Side effects reported with ondansetron were mild, and consisted of constipation in 4 patients and headache in 4 patients. Of note is the fact that the only patient (1/19) not receiving ondansetron experienced severe gastrointestinal toxicity (>15 emetic episodes).

The encouraging results observed in this small number of patients suggest that ondansetron is a safe, effective and well-tolerated anti-emetic agent that can be recommended in the prevention of nausea and vomiting from dacarbazine-containing chemotherapy.

Correspondence to E. Campora.
The authors are at the Department of Medical Oncology, Istituto Nazionale per la Ricerca sul Cancro, Viale Benedetto XV, 10 16132 Genova, Italy.
Received 12 Oct. 1994; accepted 31 May 1995.

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.

European Journal of Cancer Vol. 31A, No. 10, p. 1721, 1995.

0959–8049/95 $9.50 + 0.00

0959-8049(95)00310-X

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.
Received 19 Dec. 1994; accepted 31 May 1995.

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.