Pergamon

European Journal of Cancer, Vol. 32A, Suppl. 4, pp. S43–S45, 1996
Copyright © 1996 Elsevier Science Ltd. All rights reserved
Printed in Great Britain
0959–8049/96 $15.00+0.00

PII: S0959-8049(96)00317-6

Clinical Effects of Amifostine (Ethyol®) in Patients Treated with Carboplatin

G.T. Budd, R. Ganapathi, R.M. Bukowski and S. Murthy

Department of Hematology and Medical Oncology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195, U.S.A.

Amifostine is a compound that has been developed as a radio- and chemoprotectant. It is a prodrug, giving rise to the active thiol, WR-1065. Amifostine has been demonstrated to reduce the toxicity of ionising radiation, alkylating agents and platinum compounds. Preclinical studies have shown that amifostine can reduce the myelosuppression of carboplatin in a murine model tumour system without reducing the efficacy of therapy. In fact, in this model system, the antitumour effects of carboplatin against the OVCAR-3 cell line were actually greater with than without amifostine. Based on these preclinical studies, clinical trials of the combination of carboplatin and amifostine have been undertaken. A phase I trial of carboplatin and amifostine in pretreated patients demonstrated that two doses of amifostine 740 mg/m^2/dose may be safely administered with carboplatin. The maximum tolerated dose (MTD) of carboplatin that could be administered with amifostine was 500 mg/m^2, suggesting the hypothesis that amifostine increases the MTD of carboplatin from 400 to 500 mg/m^2. To test this hypothesis, a randomised trial of carboplatin 500 mg/m^2 versus carboplatin 500 mg/m^2 plus two doses of amifostine 910 mg/m^2/dose has been performed. Analysis of this trial is not complete, but initial results suggest a reduction of first-cycle thrombocytopenia, from a median platelet nadir value of 85 × 10^9 cells/l for carboplatin alone to 144 × 10^9 cells/l for the combination of carboplatin plus amifostine. Similarly, the median first-cycle granulocyte nadir was 1.6 × 10^9 cells/l without amifostine but 2.4 × 10^9 cells/l with the cytoprotectant. Neither of these first-cycle differences was statistically significant, but these effects are being maintained with repeated dosing, so that an increase in delivered cumulative carboplatin dose seems possible with the use of amifostine. These promising data indicate that continued studies of amifostine with carboplatin are justified and that the effects of amifostine on the thrombocytopenia produced by carboplatin-containing combination chemotherapy regimens should be investigated. **Copyright © 1996 Elsevier Science Ltd**

Key words: amifostine, carboplatin, cytoprotection
Eur J Cancer, Vol. 32A, Suppl. 4, pp. S43–S45, 1996

INTRODUCTION

AMIFOSTINE (WR-2721; Ethyol®) owes its origin to the Cold War efforts of the United States armed forces, which screened more than 4000 compounds for radioprotectant activity, hoping to find a compound to protect military personnel from the effects of ionising radiation [1]. Among the substances screened, amifostine was selected for development on the basis of its activity and low toxicity. Preclinical studies indicated that amifostine could protect normal tissues from the effects not only of ionising radiation, but also of alkylating agents and cisplatin. Further investigations demonstrated that these protective effects were relatively selective for normal as opposed to malignant tissues, suggesting a role for this compound in cancer therapy.

The mechanism underlying this selectivity seems related to the fact that amifostine is a prodrug that is dephosphorylated to the active thiol, WR-1065, by acid phosphatases. Differences in the distribution of alkaline phosphatase activity in normal tissues and their vasculature relative to tumour tissues, and in tissue pH, result in increased intracellular concentrations of WR-1065 in normal cells compared with malignant cells. Amifostine had been demonstrated to reduce the toxicity of cisplatin in several systems and shown to have protective effects on haematopoietic precursors. Because carboplatin has a mechanism of action very similar to that of cisplatin and because its dose-limiting toxicity is thrombopenia, we performed studies of the effects of amifostine on the toxicity and antitumour effects of carboplatin.

Correspondence to G.T. Budd.

PRECLINICAL STUDIES

In non-tumour-bearing BALB/c mice, amifostine allowed an escalation of carboplatin dose that could be administered with 5-fluorouracil (5-FU) 100 mg/kg, from 45 mg/kg for carboplatin alone to 60 mg/kg carboplatin plus amifostine [2]. Amifos-

tine significantly reduced the thrombocytopenia produced by the higher dose of carboplatin administered with 5-FU. This higher dose level achievable with amifostine was associated with greater antitumour effects than the lower dose was against colon 26 tumours in BALB/c mice. When administered with single-agent carboplatin to BALB/c mice bearing OVCAR-3 tumours, amifostine increased the maximum tolerated dose (MTD) of carboplatin 1.5-fold. Moreover, at the same dose of carboplatin, greater antitumour effects were observed with than without the coadministration of amifostine [3].

CLINICAL STUDIES

Phase I experience with carboplatin and amifostine

Based on the preclinical studies discussed above and the rationale leading to these studies, a phase I trial of the combination of amifostine and carboplatin was performed in patients with a variety of malignancies who had received no more than two prior chemotherapy regimens [4]. In this trial, as well as in subsequent trials of amifostine in combination with carboplatin, multiple doses of amifostine were administered based on the short plasma half-life of amifostine relative to that of carboplatin. Specifically, a dose of amifostine was administered 15 min before and again 2 h after administration of carboplatin. In the first phase of the study, it was demonstrated that two doses of amifostine 740 mg/m^2/dose could be safely given with carboplatin 400 mg/m^2. After the multiple-dose schedule of amifostine was determined to be well tolerated, the dose of carboplatin was escalated in successive cohorts of 4–6 patients. At a carboplatin dose of 500 mg/m^2, toxicity was tolerable; at a carboplatin dose of 625 mg/m^2, however, unacceptable haematopoietic toxicity was produced despite the use of amifostine, with 4 of 6 patients developing grade 4 thrombocytopenia (nadir platelet count $< 20 \times 10^9$ cells/l). Thus, in this previously treated patient population, the MTDs of the drugs used in combination were two doses of amifostine 740 mg/m^2/dose and carboplatin 500 mg/m^2. This trial suggested that amifostine increases the MTD of carboplatin from 400 to 500 mg/m^2. Furthermore, the observed thrombocyte nadirs were less than predicted on the basis of the calculated creatinine clearances, consistent with an amelioration by amifostine of the thrombocytopenia produced by carboplatin. Therefore, a randomised trial comparing the toxicity of carboplatin with that of carboplatin and amifostine combined was undertaken.

Additional phase I experience with the combination of amifostine and carboplatin has been provided by the European Organization of Research and Treatment of Cancer, which reported the preliminary results of a phase I trial of carboplatin and amifostine in previously untreated as well as previously treated patients [5]. In that trial, amifostine 740 mg/m^2 is being administered 15 min prior to and 2 and 4 h following the administration of carboplatin. In previously treated patients, the MTD of carboplatin that could be administered with three doses of amifostine was 500 mg/m^2, consistent with the previous phase I experience with this combination. Previously untreated patients, however, seem to tolerate higher doses of carboplatin, with the MTD of carboplatin being at least 720 mg/m^2. In addition, the effect of adding treatment with a haematopoietic growth factor to the amifostine–carboplatin combination is being studied in this trial.

Thus, phase I studies of the combination of amifostine and single-agent carboplatin suggest that amifostine increases to 500 mg/m^2 the MTD of carboplatin that can be administered to previously treated patients and that the MTD may be higher in previously untreated patients. These results were of sufficient interest to conduct a randomised trial of carboplatin with and without amifostine.

Controlled trials of carboplatin and amifostine

Among the early experiences with amifostine in a carboplatin-containing chemotherapy regimen is a non-randomised, sequential cohort trial of therapy with the combination of carboplatin and cisplatin, either alone or with amifostine [6]. Initially, 7 patients were treated with 28-day cycles of carboplatin 300 mg/m^2 on day 1 and cisplatin 100 mg/m^2 on day 3. In a subsequent trial, the same doses and schedule of carboplatin and cisplatin were administered, with amifostine administered prior to and 2 h after carboplatin and once prior to the administration of cisplatin. Significant reductions in grade 2–4 granulocytopenia and thrombocytopenia were observed in patients receiving amifostine. Further, no treatment delays were necessary in the group receiving amifostine, compared with a mean delay of 16.2 days in 14 of 28 cycles of carboplatin or cisplatin alone. Although these results were obtained in different groups of patients, they are consistent with an amelioration of the haematopoietic toxicity of the carboplatin–cisplatin combination by amifostine.

In a randomised trial of amifostine plus carboplatin versus carboplatin alone, patients with a variety of malignancies who had received 0 or 1 prior chemotherapy regimen, including adjuvant therapy, were randomly assigned to treatment with carboplatin 500 mg/m^2 alone or the combination of carboplatin 500 mg/m^2 and amifostine 910 mg/m^2 administered twice, once 15 min prior to carboplatin and again 2 h after the administration of carboplatin [7]. Nausea and vomiting were more severe in the amifostine-treated patients, but were manageable in all cases. Hypotension was generally noted to reverse within 5 min of interrupting the amifostine infusion, but did not reverse within 5 min in 14 of 82 courses of therapy. Preliminary results reported the median thrombocyte nadir observed during the first cycle of therapy was 85×10^9 cells/l for the 20 patients treated with carboplatin alone and 146×10^9 cells/l for the 17 patients treated with the combination of carboplatin and amifostine. This difference was not statistically significant, however, because of the small number of patients and the variability of the thrombocyte nadir. Further analyses demonstrated that amifostine treatment allowed a statistically significantly higher cumulative dose of carboplatin to be administered. Thus, the results of this trial are consistent with a chemoprotective effect for amifostine with respect to the haematopoietic toxicity of carboplatin because the thrombocytopenia produced in this trial was not particularly severe. It appears that patients with no prior therapy would tolerate higher doses of carboplatin than were given in this study.

Investigators in the United Kingdom have performed a randomised phase II trial in patients with nonsmall-cell lung cancer. This study compared carboplatin alone at a dose of 600 mg/m^2 with the combination of carboplatin 600 mg/m^2 and multiple doses of amifostine [8]. In this trial, all patients were initially treated with one cycle of carboplatin at a dose of 600 mg/m^2. After completing this course, patients were randomised to receive three additional cycles of either carboplatin 600 mg/m^2 alone or carboplatin 600 mg/m^2 in combination with three doses (pre-, 2 h post-, and 4 h postcarboplatin) of amifostine, at a dose of either 683 or 910 mg/m^2. Because treatment with three doses of amifostine 910 mg/m^2 dose was

associated with hypotension in the first 6 patients, subsequent patients were treated with three doses of amifostine 683 mg/m^2/dose. Overall, some degree of hypotension was noted in 15 of 20 courses of therapy, leading to a temporary cessation of the amifostine infusion in 12 courses and discontinuation of therapy for that cycle in three courses. Other toxicities included flushing, nausea, vomiting and sneezing. In this trial, the median platelet nadir after the first cycle, when single-agent carboplatin was administered to all patients, was 26 $\times$ 10^9 cells/l for patients subsequently randomised to receive carboplatin plus amifostine and 34 $\times$ 10^9 cells/l for patients subsequently randomised to continue therapy with carboplatin alone. In the randomised portion of the trial, the median thrombocyte nadirs did not differ between the two arms (21 $\times$ 10^9 cells/l for carboplatin plus amifostine versus 23 $\times$ 10^9 cells/l for carboplatin alone), but the median time to recovery of a platelet count of $\geq$ 100 $\times$ 10^9 cells/l was significantly shorter for patients receiving amifostine (13.5 days) than for patients receiving carboplatin alone (21.0 days; $P = 0.04$, 1-sided Wilcoxon's test). While no statistically significant difference could be demonstrated in the depth or duration of neutropenia experienced in the two treatment arms, patients receiving amifostine versus not were reported to have fewer infections (15% of courses versus 40%; $P = 0.07$) and fewer hospitalisations for infections (0 versus 24%; $P = 0.06$). Of interest was the observation of a suggestively higher response rate among the patients receiving the combination of amifostine and carboplatin than in the patients receiving single-agent carboplatin: 5 of 10 patients with assessable disease receiving amifostine plus carboplatin achieved partial responses versus 2 of 9 in the carboplatin-alone arm. Similarly, the median survival for patients treated with the combination of amifostine and carboplatin was 14 months, compared with nine months for patients treated with carboplatin alone. Thus, consistent with the preclinical experience, no evidence of tumour protection was seen in this clinical trial.

Effects of amifostine on the pharmacokinetics of carboplatin

In the initial phase I trial of amifostine and carboplatin, carboplatin pharmacokinetic studies were performed in 4 patients [4]. These studies showed considerable interpatient variability, as would be expected in a heterogeneous phase I patient population, but major pharmacokinetic parameters were not greatly different than those previously reported in patients receiving carboplatin alone, allowing the conclusion that major changes in carboplatin pharmacokinetics were not responsible for the apparent cytoprotective effects of amifostine; that is, the reduced toxicity of carboplatin when given with amifostine was not because of enhanced excretion of the cytotoxic agent.

CONCLUSION

Carboplatin is an important chemotherapeutic agent whose dose-limiting toxicity, thrombocytopenia, is one for which no prophylactic therapy other than transfusion currently exists. The potential of amifostine to attenuate this toxicity is therefore of clinical significance because it would increase the therapeutic window for carboplatin, allowing reduced toxicity or, in situations in which dose proves to be important, increased efficacy. No evidence of tumour protection of the cytotoxicity of carboplatin by amifostine has been present in preclinical or clinical studies performed to date. In fact, both preclinical and clinical data suggest the possibility that the therapeutic effects of carboplatin might be enhanced by the coadministration of amifostine. Further trials will be needed to address fully the toxicity and efficacy of this promising combination.

1. Schuchter LM, Luginbuhl WE, Meropol NJ. The current status of toxicity protectants in cancer therapy. *Semin Oncol* 1992, **19**, 742–751.
2. van Laar JA, van der Wilt CL, Treskes M, van der Vijgh WJ, Peters GJ. Effect of WR-2721 on the toxicity and antitumour activity of the combination of carboplatin and 5-fluorouracil. *Cancer Chemother Pharmacol* 1992, **31**, 97–102.
3. Treskes M, Boven E, van de Loosdrecht AA, *et al.* Effects of the modulating agent WR-2721 on myelotoxicity and antitumour activity in carboplatin-treated mice. *Eur J Cancer* 1994, **30A**, 183–187.
4. Budd GT, Ganapathi R, Bauer L, *et al.* Phase I study of WR-2721 and carboplatin. *Eur J Cancer* 1993, **29A**, 1122–1127.
5. Vermorken JB, Punt CJA, Eeltink CM, *et al.* Phase I trial of carboplatin and amifostine (abstract). *Proc Amer Assoc Cancer Res* 1995, **36**, 240.
6. Delaflor-Weiss E, Blommaert F, Gill I, *et al.* Amifostine protects from bone marrow toxicity of combinations of cisplatin and carboplatin without decreasing platinum-DNA adduct formation (abstract). *Eighth NCI-EORTC Symposium on New Drugs in Cancer Therapy*. Amsterdam, The Netherlands. 1994, **8**, 125.
7. Budd GT, Bukowski RM, Murthy S, *et al.* Randomized trial of carboplatin vs. carboplatin + amifostine in advanced malignancy (abstract). *Proc Amer Soc Clin Oncol* 1994, **13**, 442.
8. Betticher DC, Anderson H, Ranson M, *et al.* 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.