Eur J Cancer Clin Oncol, Vol. 21, No. 9, pp. 1015-1018, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00

Nephrotoxicity of High-dose Intracavitary Cisplatin with Intravenous Thiosulfate Protection*

MAURIE MARKMAN,†‡ STEPHEN CLEARY and STEPHEN B. HOWELL§

Department of Medicine, Cancer Center and General Clinical Research Center, University of California, San Diego, School of Medicine, La Jolla, CA 92093, *U.S.A.*

Abstract—*Sodium thiosulfate has been shown experimentally to protect against cisplatin-induced renal insufficiency by inactivating the nephrotoxic as well as cytotoxic properties of the agent. However, significant plasma levels of 'active' cisplatin have been demonstrated following high-dose intracavitary cisplatin administration with simultaneous intravenous thiosulfate delivery. At the UCSD Cancer Center* 131 *pateints have been treated with a total of* 485 *courses (median per patient,* 3; *range* 1-18) *of intrapleural or intraperitoneal cisplatin with intravenous thiosulfate protection. Seventy-six patients* (58%) *had previously been treated with intravenous cisplatin. A total of* 14 *courses* (2.9%) *of intracavitary therapy were complicated by a serum creatinine rise to* >1.5 mg% *which, in all but three cases, returned to the normal range within* 1 month *following treatment. All but one patient demonstrating clinical evidence of nephrotoxicity had been heavily pretreated with cisplatin. We conclude that thiosulfate can protect against clinically significant cisplatin-induced nephrotoxicity by cisplatin delivered in high doses via the intracavitary route.*

INTRODUCTION

WHILE the incidence of cisplatin-induced nephrotoxicity has decreased significantly with greater experience using this important anti-neoplastic agent, there remains a serious concern about inducing renal dysfunction when cisplatin is administered in high does [1]. In an effort to improve the efficacy of therapy of tumors principally confined to body cavities, investigators at the UCSD Cancer Center have administered a total of 485 courses of high-dose cisplatin (100 or 200 mg/m^2) intrapleurally or intraperitoneally to 131 patients along with the simultaneous intravenous administration of sodium thiosulfate, an agent demonstrated experimentally to neutralize both the nephrotoxic and cytotoxic properties of cisplatin [2, 3]. This report documents our experience with the development of clinically significant nephrotoxicity in this patient population.

MATERIALS AND METHODS

A total of 131 patients (male:female, 28:103) with a median age of 54 yr (range, 19-80 yr) were treated on one of several intracavitary protocols at the UCSD Cancer Center [4-8]. Eighty-four patients had ovarian carcinoma, 18 malignant mesothelioma and 29 a mixture of other solid tumors. Seventy-six patients (58%) had previously been treated with intravenous cisplatin before entry onto this experimental program (median dose per patient, 480 mg/m^2; range, 100-1600 mg/m^2). Study entrance criteria included a normal serum creatinine (≤1.5 mg% in our laboratory), although patients with renal dysfunction following intravenous cisplatin were not excluded if their serum creatinine was normal when they were being considered for entry onto study.

Accepted 24 January 1985.
*Supported by grants CA 23100 and 35309 from the National Cancer Institute and by grant RR-00827 from the National Institutes of Health, Division of Research Resources. This work was conducted in part by the Clayton Foundation for Research-California Division.
†To whom requests for reprints should be addressed at: UCSD Medical Center, Division of Hematology/Oncology, H-811K, 225 Dickinson Street, San Diego, CA 92103, U.S.A.
‡American Cancer Society Junior Faculty Clinical Fellow.
§Clayton Foundation Investigator.

Nineteen patients received only intrapleural therapy while two patients were treated both intrapleurally and intraperitoneally. The remainder of the patients were treated via the intraperitoneal route only. A total of 485 courses of intracavitary cisplatin-based therapy were administered (median/patient, 3; range, 1–18), of which 302 were delivered at 100 mg/m² and 183 at 200 mg/m². All courses of intrapleural cisplatin were delivered at the 100 mg/m² dose level because of solubility problems with this agent in the small treatment volume (250 ml).

The details of the four intracavitary programs employed in this patient population have been presented elsewhere [4–8]. In addition to cisplatin, 115 patients also received cytarabine, 31 patients doxorubicin and 22 patients bleomycin. Patients treated intraperitoneally at the 200 mg/m² dose level of cisplatin and some treated at 100 mg/m² received 2 l. of intravenous hydration with 5% dextrose/one-half normal saline over the 12 hr preceding cisplatin instillation. Patients receiving intrapleural therapy (100 mg/m²) as well as the remaining patients treated intraperitoneally at 100 mg/m² were given 1 l. of intravenous hydration over the hour prior to cisplatin instillation. In addition to hydration, all patients received an intravenous bolus (4 g/m² in 250 ml sterile water over 15 min) as well as an infusion (12 g/m² in 1 l. sterile water over 6 hr) of sodium thiosulfate beginning at the time of cisplatin instillation into the body cavity. One final liter of hydration was administered at the completion of the thiosulfate infusion in patients receiving the 200 mg/m² dose of cisplatin. Additional fluids were administered as clinically indicated. Patients with mesothelioma were treated weekly for 3 weeks with a subsequent 3-week rest period before resuming weekly therapy. All other patients were treated at approximately 28-day intervals.

RESULTS

As we were principally concerned with the development of clinically relevant nephrotoxicity, creatinine clearances were not routinely obtained and we used serum creatinines as a measure of cisplatin-induced renal dysfunction. Of the 485 courses of intracavitary chemotherapy administered to the patient population described above, 14 (2.9%) were associated with a serum creatinine rise to >1.5 mg%. Abnormal creatinine elevations were noted following three courses (1.0%) with cisplatin administered at 100 mg/m² and 11 courses (5.9%) with the drug given at 200 mg/m². Following only two courses (0.4%) did the serum creatinine rise to >3.0 mg%. One course was associated with serious nephrotoxicity, with a serum creatinine of 8.0 mg%. While the patient did not require dialysis and the serum creatinine has decreased, it has not returned to normal during several months of follow-up. With two additional exceptions, the serum creatinine elevations returned to the normal range within 1 month following therapy. In these two cases abnormal creatinine values returned to normal in 6 and 16 weeks following treatment.

All but one patient exhibiting evidence of clinical nephrotoxicity had been heavily pretreated with intravenous cisplatin. The median total amount of cisplatin received prior to the development of abnormal serum creatinine elevations on the intracavitary program was 865 mg (range, 0–2160 mg). Sterile pyruria was also observed in patients receiving high cumulative doses of cisplatin. However, there has been no evidence of deterioration of renal function in any patient following the completion of the experimental treatment program.

There was no difference in nephrotoxicity in patients receiving the 100 mg/m² dose of cisplatin between those who received 2 l. of overnight hydration or those who were given 1 l. over 1 hr prior to the initiation of therapy.

DISCUSSION

Sodium thiosulfate is one of several thio-containing analogs which have been demonstrated *in vitro* and *in vivo* to prevent certain toxic effects of cisplatin, including cisplatin-induced nephrotoxicity [2, 3, 9]. It has been suggested that these compounds might act by blocking or reversing cisplatin-DNA cross-linking or by forming complexes with cisplatin, thereby preventing entry into cells [10, 11].

Unfortunately, a major concern with the use of such protective agents is that they will also neutralize the cytotoxic properties of this most effective chemotherapeutic agent. In a phase I trial of escalating doses of intraperitoneally administered cisplatin with sodium thiosulfate delivered simultaneously intravenously to protect against cisplatin-induced renal dysfunction, the dose of cisplatin was able to be escalated to 270 mg/m² without the production of significant nephrotoxicity [12]. As predicted by a mathematical model suggesting a major pharmacokinetic advantage for peritoneal cavity exposure to cisplatin compared to that of the systemic circulation when the drug is delivered via the intraperitoneal route, the peak concentration and AUC (area under the concentration vs time curve) were significantly higher for the peritoneal cavity than the plasma [13]. Somewhat surprisingly, however, the AUC for the plasma (at an intraperitoneal dose of 270 mg/m²) to 'active'

cisplatin (not bound to thiosulfate) was *twice* that observed when cisplatin is administered intravenously at a dose of 100 mg/m^2 without thiosulfate [12, 14, 15]. Thus, while a certain amount of cisplatin is clearly being inactivated upon entry into the plasma when thiosulfate is present, the exposure of the systemic circulation to 'active' drug is substantial when cisplatin is delivered in the high doses given to our patient population.

Protection from the nephrotoxic effects of cisplatin with the simultaneous use of thiosulfate is not absolute. While overall less than 3% of courses were associated with serum creatinine rises out of the normal range, several patients did develop significant renal dysfunction, including a single patient who experienced serious renal insufficiency. In addition, the fact that we were able to deliver high doses of intracavitary cisplatin to this large patient population, many of whom had previously been treated with cisplatin, does not necessarily mean that similar protection will occur if the cisplatin is administered intravenously in high doses. In a group of heavily pretreated patients participating in a phase I trial of escalating doses of intravenous cisplatin with intravenous thiosulfate (delivered simultaneously in different arms), cisplatin-induced nephrotoxicity was a more serious problem [15]. However, a significant increase in exposure of the systemic circulation to 'active' drug was demonstrated in this trial and it remains to be determined how serious the toxic effects of this regimen will be in previously untreated patients.

In conclusion, we have demonstrated that thiosulfate can protect against cisplatin-induced renal dysfunction when this agent is delivered in high doses (100 or 200 mg/m^2) via the intracavitary route. Perhaps most impressive is the fact that most of our patients had been extensively pretreated with intravenous cisplatin. The question of whether thiosulfate can be protective when cisplatin is administered in standard 'high' doses intravenously without interfering with the cytotoxic properties of this agent will require careful pharmacokinetic and clinical evaluation.

REFERENCES

1. Leohrer PJ, Einhorn LH. Cisplatin. *Ann Intern Med* 1984, **100,** 704-713.
2. Howell SB, Taetle R. Effect of sodium thiosulfate on *cis*-dichlorodiammineplatinum(II) toxicity and antitumor activity in L1210 leukemia. *Cancer Treat Rep* 1980, **64,** 611-616.
3. Iwamoto Y, Kawano T, Uoxumi J, Aoki K, Baba T. "Two-route chemotherapy" using high-dose ip cisplatin and iv sodium thiosulfate, its antidote, for peritoneally disseminated cancer in mice. *Cancer Treat Rep* 1984, **68,** 1367-1373.
4. Markman M, Howell SB, Green MR. Combination intracavitary chemotherapy for malignant pleural disease. *Cancer Drug Deliv* 1984, **1, 333**-336.
5. Markman M, Howell SB, Lucas WE, Pfeifle CE, Green MR. Combination intraperitoneal chemotherapy with cisplatin, cytarabine, and doxorubicin for refractory ovarian carcinoma and other malignancies principally confined to the peritoneal cavity. *J Clin Oncol* 1984, **2,** 1321-1326.
6. Pfeifle CE, Howell SB, Markman M. Intracavitary cisplatin chemotherapy for mesothelioma. *Cancer Treat Rep* In press.
7. Markman M, Howell SB. Intraperitoneal chemotherapy for ovarian carcinoma. In: Alberts D, Surwitt E, eds. *Gynecological Oncology*. Boston, MA, Martinus Nijhoff, In press.
8. Markman M. Intracavitary chemotherapy. *CRC Crit Rev Oncol Hematol* In press.
9. Burchenal JH, Kalaher K, Dew K, Lokys L, Gale G. Studies of cross-resistance, synergistic combinations and blocking of activity of platinum derivatives. *Biochimie* 1978, **60,** 961-965.
10. Filipsik J, Kohn KW, Prather R, Bonner WM. Thiourea reverses cross-links and restores biological activity in DNA treated with dichlorodiamminoplatinum(II). *Science* 1979, **204,** 181-183.
11. Uozumi J, Ishizawa M, Iwamoto Y, Baba T. Sodium thiosulfate inhibits *cis*-diamminedichloroplatinum(II) activity. *Cancer Chemother Pharmacol* 1984, **13,** 82-85.
12. Howell SB, Pfeifle CL, Wung WE *et al.* Intraperitoneal cisplatin with systemic thiosulfate protection. *Ann Intern Med* 1982, **97,** 845-851.
13. Dedrick RL, Myers CE, Bungay PM, DeVita VT Jr. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. *Cancer Treat Rep* 1978, **62,** 1-11.

14. Belt RJ, Himmelstein KJ, Patton TF, Bannister SJ, Sternson LA, Repta AJ. Pharmacokinetics of non-protein-bound platinum species following administration of *cis*-dichlorodiammineplatinum(II). *Cancer Treat Rep* 1979, **63**, 1515–1521.
15. Pfeifle CE, Howell SB, Felthouse RD, Woliver TBS, Markman M. High-dose cisplatin with sodium thiosulfate. *J Clin Oncol* In press.