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Short Communications

Audiological findings in a Phase I protocol investigating the effect of WR 2721, high-dose cisplatin and radiation therapy in patients with locally advanced cervical carcinoma

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Abstract
WR 2721 (ethiofos) protects against the toxic effects of the heavy metal compound cisplatin, which is used in the treatment of solid tumours. In a Phase I protocol designed to determine the maximum dose of WR 2721 which could be tolerated when administered in combination with cisplatin and radiation therapy to patients with cervical carcinoma, 11 patients were evaluated by audiologic testing before and after cisplatin WR 2721 administration in an attempt to identify the degree of ototoxicity. Forty-five per cent were noted to have significant hearing threshold changes, predominantly in the high frequencies. There were no significant changes in the speech frequencies in this series. This contrasts with the greater degrees of ototoxicity observed in controls treated in the same way who received cisplatin without WR 2721 protection.

Key words: Cisplatin; Ototoxicity; Hearing loss, sensorineural; Audiometry

Introduction

This study results from a Phase I protocol designed to investigate the maximum dose tolerated and the feasibility of a novel regime of the chemoprotective agent WR 2721 in combination with high-dose cisplatin (CDDP) and radiation therapy in the treatment of locally advanced carcinoma of the cervix (Wadler *et al.* 1993).

Cisplatin is known to cause neurosensory hearing loss which is both dose (Piel *et al.*, 1974; Fleming *et al.*, 1985) and schedule dependent (Vermorken *et al.*, 1983; Blumenreich *et al.*, 1985). High frequency hearing loss usually occurs at a cumulative dose of 200 mg/m^2 or higher (Fleming *et al.*, 1985). In this study a cumulative dose of 400 mg/m^2 was administered; thus high frequency hearing loss was anticipated.

The organic thiophosphate WR 2721 (ethiofos; NSC 296961) prevents the toxicity to normal tissues caused by chemotherapy and radiation in tumour-bearing rodents (Yuhas and Culo, 1980; Yuhas *et al.*, 1980a; Yuhas *et al.*, 1980b). In human clinical Phase I and II trials of WR 2721, 740–910 mg/m^2 administered prior to 60–150 mg/m^2 of CDDP as a 30 minute infusion every three to four weeks protected against the neurotoxicity of cisplatin without diminishing the antitumour effects (in patients with advanced melanoma or ovarian carcinoma) (Glover *et al.*, 1987; Glick *et al., 1992).*

Reports in the literature do not demonstrate consistent protection from ototoxicity through the use of WR 2721 (Glover *et al.*, 1987; Gandara *et al.*, 1991). It was felt that our group of patients, although small, would be of interest in this respect.

Materials and methods

All patients enrolled in this study had histologically-proven, locally advanced carcinoma of the uterine cervix. Patients were required to have had no prior chemotherapy or radiotherapy, to have adequate renal, bone marrow and hepatic function, no active infection, and to be able to give written informed consent.

Cisplatin was administered at 20 mg/m^2 daily (× 5) beginning on Day 1 and 22 of the trail following adequate hydration with at least 2l of normal saline. It was administered concurrently with pelvic radiation. Following each brachytherapy treatment, which began about two weeks after external beam therapy was concluded, 100 mg/m^2 of CDDP was administered as a single 30 minute infusion preceded by adequate hydration. The total dose of cisplatin for all patients was 400 mg/m^2.

WR 2721 was administered over 15 minutes immediately prior to the cisplatin infusion. As this study sought to determine the maximum dose of WR 2721 tolerated when administered in combination with cisplatin and radiation therapy, the dose of WR 2721 was raised between cohorts of patients from 340 to 910 mg/m^2.

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Audiologic studies

Audiometric procedures were performed in a sound-proofed booth with a Grason Stadler GSI No. 16 Audiometer. Frequencies tested in each ear included 250, 500, 1000, 2000, 4000 and 8000 Hz (except in one patient in whom 250 and 500 Hz could not be tested).

When more than one post-treatment audiogram was available, the most recent was used for evaluation. For consistency of reporting, findings from air conduction were utilized for reporting results (Laurell and Jungnelius, 1990). Speech pure tone averages were obtained by averaging the results obtained in the frequencies of 500, 1000 and 2000 Hz.

Significant hearing loss was classified in accordance with the criteria of Laurell and Jungnelius (1990), by a decrease of 10 dB at three frequencies in the ear, or a decrease of 15 or more decibels at any one frequency. Severity of hearing loss was classified in accordance with the criteria of Aguilar-Markulis *et al.* (1981) in the following manner: no ototoxicity, < 10 dB change in all frequencies; suspect ototoxicity, ≥ 10 and ≤ 15 dB in any one frequency; mild ototoxicity, ≥ 10 and ≤ 20 dB in any two frequencies, or, ≥ 15 and ≤ 20 dB in both ears at any one frequency; moderate ototoxicity, > 20 and ≤ 40 dB at 4000 or 8000 Hz; marked ototoxicity, > 40 dB at 4000 or 8000 Hz; severe ototoxicity, > 40 dB at 4000 or 8000 Hz and > 25 dB at 500, 1000 or 2000 Hz.

Results

Eleven patients completed the pre- and post-treatment audiologic evaluation. Ten out of the 11 patients could be evaluated at all frequencies studied (250–8000 Hz) as in one patient 250 and 500 Hz could not be tested.

Significant hearing loss by the Laurell and Jungnelius (1990) criteria was noted in nine ears (41 per cent) in five patients tested (45 per cent). One ear of two patients had a hearing loss fulfilling the criteria of a 10 dB threshold shift at three frequencies. All of the ears with significant hearing loss fulfilled the criteria of ≥ 15 dB loss at one frequency; all these patients had this loss in the high frequencies at 4000 or 8000 Hz. One patient with a loss of ≥ 15 dB at 4000 Hz also had a loss of ≥ 15 dB at 250 Hz in one ear.

Severity of ototoxicity as defined by Aguilar-Markulis *et al.* (1981) was noted in the following number of patients: no ototoxicity or suspect ototoxicity in five; mild ototoxicity in three; moderate ototoxicity in two; marked ototoxicity in one and severe ototoxicity in none of the patients. The three patients in this study with moderate or marked ototoxicity had bilateral loss.

The total number of patients with ototoxicity is plotted by frequency in Figure 1. Overall mean hearing change (in dB) is recorded in Figure 2. No significant mean hearing change was noted at the low speech frequencies. At 4000 Hz a mean hearing loss of 4.3 dB was noted and at 8000 Hz a mean hearing loss of 10.7 dB was observed.

The mean speech pure tone average was similar between the pre- and post-treatment groups, the mean average difference between the two groups being only 0.2 dB.

Discussion

The ototoxic potential of cisplatin is well established (Nakai *et al.*, 1982; Moroso and Blair, 1983; Fleming *et al.*, 1985; Vodvarka *et al.*, 1985; Kopelman *et al.*, 1988, Laurell and Jungnelius, 1990; Weatherly *et al.*, 1991). The reported incidence varies widely in various series from 11 to 100 per cent (Weatherly *et al.*, 1991). The overall incidence is felt to be approximately 69 per cent (Moroso and Blair, 1983).

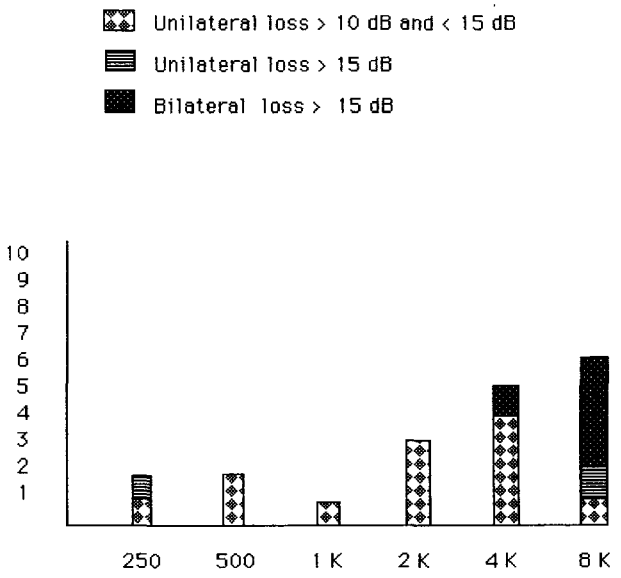

FIG. 1
Number of patients with hearing loss post-treatment by frequency (air conduction).

Cisplatin toxicity tends to be characterized by symmetric high frequency hearing loss (Reddel *et al.*, 1982; Moroso and Blair, 1983; Melamed *et al.*, 1985). With continued exposure, the speech frequencies can become involved (Schaefer *et al.*, 1985; Weatherly *et al.*, 1991). It is generally accepted that there is a direct relationship between cisplatin ototoxicity and cumulative dose (Piel *et al.*, 1974; Reddel *et al.*, 1982). High frequency hearing loss occurs almost invariably at cumulative doses above 200 mg/m^2 (Helson *et al.*, 1978) The dose used in this study, 400 mg/m^2, is a high-dose therapy.

In this study 45 per cent of patients tested had significant high frequency hearing loss. There were no significant elevations of the speech reception thresholds. This compares quite favourably with several other published studies in which, by this cumulative dose, upwards of 65 per cent of patients had significant high frequency hearing losses (Helson *et al.*, 1978; Mahoney *et al.*, 1983; McHaney *et al.*, 1983; Vermoken *et al.*, 1983; Melamed *et al.*, 1985; Kopelman *et al.*, 1988; Weatherly *et al.*, 1991).

The mechanism by which WR 2721 confers selective protection appears to be in part related to its differential absorption in normal and in malignant tissues. Selective protection by WR 2721 results from hydrolysis at the cell membrane to the active metabolite WR 1065 due to higher levels of alkaline phosphatases in normal cells (Calabro-Jones *et al.*, 1985; Gardara *et al.*, 1991). A second factor is the pH dependence of the uptake of WR 1065 by cells. The

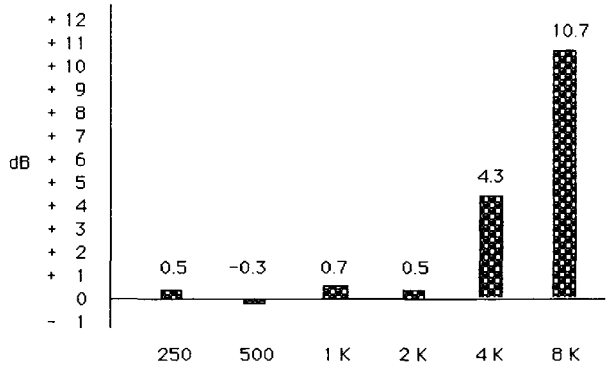

FIG. 2
Mean hearing change (dB) per ear by frequency.

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predominantly anaerobic metabolism of tumour tissues causes their pH to be lower than normal tissues. A sharp decrease in the rate of uptake of WR 1065 is seen with decreasing pH (Calabro-Jones *et al.* 1988). Detoxification of platinum then occurs as a result of the chelating properties of WR 1065 (Gandara *et al.*, 1991; Treskes *et al.*, 1992a). In an *in vitro* system using salmon sperm DNA, WR 2721 and its byproducts, WR 1065 and WR 33278, have been noted to interfere strongly with the formation of CDDP–DNA adducts (Treskes, *et al.*, 1992b).

In clinical Phase I and II trials of WR 2721, 740–910 mg/m^2 administered prior to cisplatin, protected against neurotoxicity and nephrotoxicity without diminution of the antitumour effect (Glover *et al.*, 1987; Click *et al.*, 1992) The decrease in neurotoxicity reached statistical significance ($p<0.03$) (Mollman *et al.*, 1988).

To date, clinical studies in which WR 2721 has been investigated with regard to hearing changes in patients treated with platinum have not demonstrated significant otoprotection (Glover *et al.*, 1987; Glover *et al.*, 1989; Kemp *et al.*, 1990; Ganadara *et al.* 1991). These studies did not employ the novel daily × 5 schedule for cisplatin and WR 2721 which was used in Phase I study. The greater ratio of WR 2721 to cisplatin may have accounted for the salutary effects.

The finding in our study of ototoxicity in only 45 per cent of patients tested, and no significant ototoxicity in the speech frequencies, is encouraging and suggests the possibility that WR 2721 gave some protection to this group of patients against ototoxicity. Caution is needed not to overinterpret the favourable nature of these results on hearing loss, however: firstly, only 11 patients completed the testing (a very small sample size); secondly previous reports of cisplatin ototoxicity were in paediatric populations who may be more susceptible to the ototoxic effects of cisplatin (Weatherly *et al.*, 1991); and thirdly, there are a few series of patients receiving cisplatin at cumulative doses similar to ours with comparable hearing losses (Laurell and Borg, 1988).

Further audiological investigations are clearly necessary. Temporal bone studies in an animal model would also be helpful, in order to elucidate the degree of protection, if any, proferred by WR 2721 and its metabolites against ototoxicity used in the novel daily × 5 schedule employed in our study.

Conclusions

Eleven patients with advanced ovarian carcinoma who were treated with cisplatin, radiation therapy, and WR 2721, were evaluated by audiological testing in an attempt to identify the degree of ototoxicity. Forty-five per cent were noted to have significant hearing threshold changes, predominantly in the high frequencies. There were no significant changes in the speech frequencies in this series.

It appears that WR 2721 may have had a protective effect on the neuroepithelium of the ears in the patients in this group. Further studies are clearly needed to investigate this possibility.

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