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# Cisplatin-albumin complex for treatment of cancer of the head and neck

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**Abstract**
Many patients with cancer of the head and neck are unable to receive or continue treatment with cisplatin, which is nephrotoxic, because of poor renal function. We present here, however, the case of a patient who underwent conventional cisplatin therapy but who then had to be withdrawn from treatment because of renal toxicity despite having undergone partial remission. Treatment was then changed to cisplatin in the form of a cisplatin-albumin complex which is not nephrotoxic. The patient went on to a histologically confirmed complete response and we suggest that although the cisplatin-albumin complex may not be as effective as the conventional form of the drug it offers a possible form of treatment of patients with compromised renal function who could not otherwise be treated.

## Introduction

The single most effective drug for the treatment of head and neck carcinoma is cisplatin (*cis*-diamminedichloroplatinum (II)) (Morton *et al.*, 1985; Taylor, 1987) but its use is limited by its renal toxicity. The exact mechanism of nephrotoxicity is still a matter for conjecture—the various unbound platinum species in plasma have frequently been implicated but the total platinum load filtered by the kidney and the platinum concentration in the kidney may also be important (Uozumi and Litterst, 1988). Cisplatin forms a number of transformation products *in vivo* which rapidly become covalently bound to plasma proteins (principally albumin), and within a few hours after a dose of cisplatin the unbound (ultrafilterable) platinum has fallen to around 10 per cent or less of the total plasma platinum. One previous study (De Simone *et al.*, 1987) of cisplatin in which the drug was allowed to bind to albumin before administration showed anti-tumour activity *in vitro* and *in vivo* with much less toxicity. Since December 1988, we have treated 38 patients with end-stage head and neck carcinoma with a cisplatin-albumin complex in a phase 1 study. Patients who were unfit for conventional cisplatin treatment owing to impaired renal function were entered into the trial. The dose of cisplatin in this study has been increased serially from 100 mg/m$^2$ to 650 mg/m$^2$. We have seen 2/38 complete responses and now wish to present one which has full histological confirmation.

## Case report

A 73-year-old lady was treated elsewhere with irradiation in July 1986 for a $T_3N_0M_0$ transglottic laryngeal carcinoma. In March 1988, she needed a tracheostomy and subsequent total laryngectomy for local recurrence. She was then referred to us for closure of a pharyngo-cutaneous fistula. The patient was well until September 1989 when she complained of bleeding due to a swelling (2 × 2 cm) around her stoma caused by a second local recurrence. The part of the tumour inside her stoma was debulked and she had two courses of cisplatin (the first course was 100 mg/m$^2$ and the second only 50 mg/m$^2$ owing to renal toxicity arising from the first dose). Despite the fact that she had a partial remission we had to discontinue treatment because of nephrotoxicity shown by a decrease of creatinine clearance from 60 to 35 ml/min. She was treated with three courses of the cisplatin-albumin complex, prepared as previously described (Lindup *et al.*, 1990; Holding *et al.*, 1992), at a dose of 625 mg/m$^2$. No pre- or post-hydration was given and no prophylactic antiemetic. She did suffer some mild nausea and vomiting which was easily treated with metoclopramide administered intravenously. No other side-effects were observed. Her creatinine clearance, taken at her third course of the complex, had improved to 50 ml/min. No tumour could be detected on examination after this third course and flexible endoscopies showed only a benign web at 4 cm below her stoma. A recent CT-scan of the neck and superior mediastinum showed no tumour or enlarged lymph nodes, while biopsies taken at three successive monthly intervals from both inside and outside the stoma showed granulation tissue with no evidence of tumour. The patient has now maintained a complete response for more than four months.

## Discussion

This complex of cisplatin is probably not as effective as cisplatin itself but it may be useful for patients with poor renal function. Furthermore the patients need only stay in hospital overnight and almost none of them complain of nausea or vomiting. The complex therefore offers a better quality of life with regard to drug treatment in the last days of patients with end-stage disease.

It is normally considered that it is only the fraction of drug in the bloodstream which is unbound that is pharmacologically active (Lindup, 1987), and so the cisplatin—albumin complex (where the platinum is covalently bound) should not possess any significant therapeutic activity because the concentration of unbound platinum is only 1.2 per cent of the total (Holding *et al.*, 1992). This view may have to change, however, because doxorubicin covalently coupled to albumin also possesses antitumour activity (Cummings *et al.*, 1991). There is evidence that macromolecules such as albumin may permeate the interstitial

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fluid of tumours more readily than that of normal tissue (Gerlowski and Jain, 1986). These drug complexes may therefore deliver a larger dose of drug to the tumour, where after degradation of the complex the therapeutic drug moiety is released.

There are important pharmaceutical aspects to the preparation of the complex, for example in relation to the time and temperature of incubation during its preparation that need to be explored. The particular type of albumin preparation used may influence the nature of the cisplatin-albumin complex which in turn could affect the tumour uptake of the complex and/or the release of the therapeutically active platinum species. In addition appropriate microbiological quality assurance would be needed for large-scale manufacture of the complex.

If it can be established by further investigation that this complex does have sufficient efficacy then its lack of toxicity means that it could be a viable alternative to conventional cisplatin as a palliative treatment for end-stage patients with poor renal function and where other drugs or forms of treatment are not appropriate.

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