Occasional Review

Cis-platinum: a new anticancer agent

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The introduction of the platinum group of anticancer agents is a classic story of serendipity. In 1975, while investigating the effect of an electrical field on bacterial growth, Rosenberg *et al*¹ found that the replication of *Escherichia coli* was inhibited by an electrical current passed between platinum electrodes. They later found that this growth inhibition was not caused by the electrical current, but by several platinum compounds formed in the medium. Subsequent investigation of these compounds led to the identification of platinum diamminodichloride (*cis*-platinum; DDP) as the most active antitumour agent in animal systems. Since 1972 DDP has been available as a research drug from the National Cancer Institute in the USA, and it is now commercially available in Britain (Neoplatin; Mead Johnson). This review aims at providing clinicians with information on the optimal methods of use, the toxicity, and the antitumour effects of the drug.

Preclinical studies

MECHANISM OF ANTITUMOUR ACTION

In-vitro studies show that DDP selectively and persistently inhibits the synthesis of deoxyribonucleic acid (DNA) whereas ribonucleic acid (RNA) and protein synthesis is relatively spared.²⁻³ Parallels have been drawn between DDP and the bifunctional alkylating agents such as the nitrogen mustards. Nevertheless, evidence of the amount of cross-linking at toxic doses⁴ suggests that, although cross-linking does occur, it is not responsible alone for the antitumour activity. DDP will kill cells at any stage in their growth cycle.

PHARMACOKINETICS

Initial studies of the pharmacokinetics of DDP using radiolabelled platinum or flameless atomic absorption spectrometry measured total platinum concentrations. Studies on dogs⁵ showed a biphasic plasma-decay curve with an initial half life of about 22 minutes and a terminal half life of nearly five days. High tissue concentrations were found in the kidney, liver, ovary, testis, and uterus with tissue to plasma ratios of up to 4:1.

Measurement of DDP plasma concentrations by flameless atomic absorption spectrometry⁶ shows that a biphasic plasma-decay pattern also occurs in man after bolus administration. The initial half life is about 30 minutes and the terminal half life four to five days. Urinary excretion is incomplete (30% at 48 hours). After infusions given over 24 or 48 hours DDP reaches maximum plasma concentrations at the end of the infusion and the concentration then falls slowly. Urinary excretion is again incomplete (20% at 48 hours). DDP is rapidly

bound to plasma, however, and studies measuring "free" DDP show that much of the initial fall in concentration after a bolus dose is due to tissue binding of the drug. Three hours after giving DDP only about 10% of the dose remains unbound and therefore potentially active.⁷

Studies in man measuring "free" platinum species have shown a terminal half life of 30-50 minutes after bolus injection,⁷ emphasising the probability that the 30-minute initial half life found when measuring total DDP reflects distribution and not excretion of the drug. DDP is detectable in the tissues for long periods after a single injection, and low urinary concentrations may be found in patients up to one month after treatment.⁶

Mode of administration

Schedules for treating patients have included: daily bolus injections for five days, a five-day continuous infusion, 24-hour and 48-hour infusions, and injection of a single bolus. Courses are usually repeated after three weeks. Despite the multiplicity of treatment schedules there is no evidence that any one is more efficacious.

Nephrotoxicity (discussed below) limits the dose, and it is of paramount importance that DDP is given with careful hydration.⁸ Fluid supplements (given by infusion) are mandatory, though the volume necessary and the optimum duration are not clearly defined. As a guide it is advisable to start the infusion at least two hours before giving DDP and to continue for at least six hours after administration is complete. The rate of infusion should be sufficient to maintain a urine output of over 200 ml/hour and continue until vomiting stops and oral fluids are tolerated. Mannitol⁹ and frusemide¹⁰ have been used in addition to hydration, though their roles are undefined and saline infusions alone may be equally effective.¹¹

Presentation

DDP is supplied in 10 mg amber phials. The DDP is dissolved in 10 ml sterile water for injection. Unopened phials of the dry powder should be stored in a refrigerator (4°C) for not more than two years. The reconstituted solution is stable at room temperature for 20 hours. Once reconstituted, the solution should be kept at room temperature, as refrigeration will cause precipitation.

Antitumour activity

TESTICULAR CANCER

DDP was first shown to be an effective antitumour agent in patients with non-seminomatous testicular cancer. The drug was initially used as a single agent in previously treated patients. Later studies, including those on untreated patients, showed a complete remission rate of 19% with an objective response rate of 60%.¹² Most responses were, however, short, and drug toxicity was common before hydration regimens were introduced.

DDP is probably the most active single agent in non-seminomatous testicular tumours.¹³ Einhorn and Donohue therefore combined it with the most effective regimen then available—namely, high-dose vinblastine and bleomycin. With this regimen, 33 out of 47 evaluable patients (70%) achieved complete remission.¹⁴ A further 10% of patients were rendered disease-free by operation, giving a complete

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remission rate of 80%. In their series 33 of the patients were alive and 27 disease-free 21 to 45 months¹⁵ after treatment. Cvitkovic *et al*¹⁶ reported a complex chemotherapy regimen (VAB III) that includes DDP in the induction and maintenance phases of the treatment. Out of 80 evaluable patients, 50 (63%) obtained a complete response and 70 (89%) an objective remission.

Toxicity from the regimen of Einhorn and Donohue is serious,^{14 17} and efforts to reduce this (primarily by reducing the vinblastine dose) are being made. Toxicity from the VAB III regimen is reportedly less serious,¹⁶ but comparisons between the two regimens have not been made, and both groups are continuing to improve their regimens by modifying the doses and scheduling.

OVARIAN CANCER

Alkylating agents have been the standard treatment for ovarian carcinoma for many years. Objective remissions occur in about half of patients receiving alkylating agents regardless of the alkylator used. DDP was initially shown by Wiltshaw and Kroner¹⁸ to be an effective single agent in previously treated patients. Since then DDP has been used in several combinations, most notably with adriamycin and cyclophosphamide. Ehrlich *et al*¹⁹ reported a combination of DDP (given daily for five days or in one bolus) with adriamycin and cyclophosphamide that produced 21 (72%) objective responses in 29 patients. Thirteen (45%) obtained complete responses, and in all cases the regimen was the primary treatment. Bruckner *et al*²⁰ described several regimens including DDP. Adriamycin and DDP given as initial treatment to 30 patients produced a complete response in 11 and a partial response in 13. Thiotepa and DDP produced a complete response in five out of 19 patients and a partial response in seven. Cyclophosphamide, adriamycin, and DDP produced 12 objective responses in 24 patients previously treated.²¹ Ehrlich *et al* are currently using a regimen (CHAP) which includes DDP, hexamethylmelamine, adriamycin, and cyclophosphamide. The use of a similar combination (CHAP) was reported by Kane *et al*.²² All patients had received previous treatment with alkylating agents, and out of 22 evaluable patients 4 (18%) responded completely and 7 (32%) responded partially.

In Southampton we used a combination of adriamycin, cyclophosphamide, and DDP in a pilot study. Out of 16 evaluable patients, 11 (69%) achieved a clinical complete remission and three a partial remission. These various combinations appear to be much more effective induction regimens than single alkylating agents (which produce a complete remission rate of about 15%), but it remains to be seen whether these remissions will be durable. Controlled trials comparing such combinations with standard treatment are needed. These must use survival and not remission as the prime criterion.

BLADDER CANCER

Early studies by the Memorial Sloan-Kettering Cancer Centre²³ suggested that DDP is useful in bladder cancer. Further studies by the group using DDP in combination with other drugs showed impressive results, 14 out of 20 patients obtaining remission for one to over seven months.²⁴ Other studies of DDP have produced encouraging results. Williams *et al*²⁵ reported that 10 (63%) out of 17 patients obtained an objective response to a combination of DDP, adriamycin, and 5-fluorouracil, and Soloway reported remission in 60% of a small group of patients given DDP alone.²⁶ Further studies of DDP combined with other drugs are under way, and the results must be awaited before the role of DDP in this tumour can be judged.

HEAD AND NECK CANCER

Much of the initial data on the use of DDP in treating head and neck cancer were reported from the Memorial Sloan-Kettering Cancer Centre. The initial results of the use of DDP in these tumours²⁷ were confirmed in a study using high-dose DDP with hydration and mannitol diuresis.²⁸ Further reports (table) of DDP used singly and in combination suggest that DDP combined with other drugs may have a role in the management of head and neck cancer. This, however, remains to be confirmed in proper controlled trials.

OTHER TUMOURS

Early studies²⁹ suggested that DDP may be useful in neuroblastoma, which has been supported by further evidence from small series.^{30 31} DDP has also shown activity against osteogenic sarcoma,³² lymphomas,^{33 34} melanoma,³⁵ and endometrial and other gynaecological carcinomas.³⁶ It may also have some activity against breast cancer,³⁷ hepatoma,³⁴ Wilms's tumours,³¹ and thyroid cancer.³⁰ Lung cancer is apparently unresponsive to DDP, although DDP has been included in moderately effective combinations. It is also inactive against colonic cancer and acute lymphocytic leukaemia.

Toxicity

The major toxic effects caused by DDP are nephrotoxicity, nausea and vomiting, myelosuppression, ototoxicity, anaphylactic-like reactions, and neurotoxicity.

NEPHROTOXICITY

Dose-related and cumulative renal toxicity is the major dose-limiting factor and in early studies was an appreciable problem. Hydration with or without diuretics allows larger doses of DDP to be given with less nephrotoxicity. The toxicity produced by DDP is a focal acute tubular necrosis primarily affecting the distal convoluted tubules and collecting ducts.³⁸ Hydration or diuresis or both⁸⁻¹⁰ noticeably reduces the immediate renal toxicity, though cumulative toxicity may still be a problem. The renal toxicity associated with DDP is apparently permanent,³⁹ and careful monitoring of renal function is essential to avoid this potentially most serious consequence of treatment.

NAUSEA AND VOMITING

Severe nausea and vomiting are almost universal and may necessitate stopping treatment. It usually starts within one hour of treatment and lasts up to 24 hours. Continued nausea, occasional vomiting, and profound anorexia may persist for up to one week and are common. In some patients electrolyte imbalance may require correction.

OTOTOXICITY

Audiologic abnormalities occur in up to 30% of patients.⁴⁰ Hearing loss is usually confined to the frequency range above speech tones (4000-8000 Hz). Tinnitus (bilateral or unilateral) may be associated with the hearing loss, and occasional patients may have impaired ability to hear normal speech tones. The hearing loss

Results of using DDP alone or in combination with other drugs in head and neck cancer

Series	Drugs	No of evaluable patients	No (%) obtaining remission	Comments
Lippman <i>et al</i> (1973) ²⁷ Hayes <i>et al</i> (1977) ²⁸	DDP	38	10 (26)	Low dose
Jacobs <i>et al</i> (1978) ⁴⁵	DDP	18	7 (39)	High dose
Randolph <i>et al</i> (1977) ⁴⁶	DDP + bleomycin	18	12 (67)	All prior radiotherapy/surgery; 11 prior chemotherapy
Amer <i>et al</i> (1978) ⁴⁷	Vincristine, bleomycin, DDP	16	6 (38)	All prior radiotherapy/surgery
Hong <i>et al</i> (1978) ⁴⁸	Bleomycin, DDP	16	10 (63)	11 no prior treatment
Kaplan <i>et al</i> (1978) ⁴⁹	Methotrexate, bleomycin, DDP	20	12 (60)	17 prior radiotherapy/surgery
Caradonna <i>et al</i> (1978) ⁵⁰	DDP, Methotrexate, bleomycin	14	11 (79)	12 prior radiotherapy/surgery
Elias <i>et al</i> (1978) ⁵¹	DDP, Methotrexate, bleomycin	23	14 (61)	
Panethieve <i>et al</i> (1978) ⁵²	DDP	26	8 (31)	

DDP = Platinum diamminodichloride.

associated with DDP is not clearly dose-related but appears to be cumulative and occurs most commonly with high-dose regimens. There is no clear evidence of its reversibility.⁴¹

M ELOSUPPRESSION

Early experience with DDP suggested that its myelosuppressive effect was mild. Nephrotoxicity was the dose-limiting factor, however, and new studies using higher doses are increasingly reporting severe myelosuppression. Myelosuppression is dose-related⁴² and possibly cumulative.²⁷ Leucopenia and thrombocytopenia, though more often reported than in earlier studies, are not a problem when DDP is used alone, though appreciable anaemia is commonly seen and is cumulative.⁶

ANAPHYLACTIC-LIKE REACTIONS

The Investigational Drug Branch of the Division of Cancer Treatment of the National Cancer Institute in the USA has received 14 reports of anaphylactic-like reactions possibly occurring after DDP.⁴¹ These reactions consist of facial oedema, wheezing, hypotension, and tachycardia within minutes of giving DDP. All were controlled with antihistamines, corticosteroids, or adrenaline.

NEUROTOXICITY

Peripheral neuropathy associated with DDP has been reported by several groups.^{6, 18, 43} Seizures have also been reported, though these may be related to hyponatraemia consequent on the overhydration used when giving DDP. Two cases of ophthalmic toxicity (papilloedema and retrobulbar neuritis) possibly related to DDP have also been reported.⁴⁴

HYPOMAGNEAEMIA

Several recent reports have described inappropriate urinary magnesium loss in patients receiving platinum. Between 5% and 10% of patients studied have developed clinical signs (tetany, muscle cramps, and ECG abnormalities) requiring admission to hospital. Other patients have been rendered hypocalcaemic, though this has returned to normal with magnesium repletion. This hypomagnesaemia is probably secondary to a renal tubular defect in magnesium conservation.

Conclusions

DDP is the first of a unique group of antitumour agents to be used clinically. It is highly active against several solid tumours, including those of the testis, ovary, bladder, and head and neck. It also acts against other solid tumours and is undergoing further evaluation. It has a clearly established role in treating testicular germ-cell tumours, but further study is required before its role in the routine treatment of other solid tumours can be defined.

From our experience DDP produces potentially serious toxic effects. Since these are cumulative, careful monitoring of peripheral blood counts and of renal and auditory function are necessary to contain these side effects within tolerable limits. Probably the indications for this drug will extend to tumours other than those of testicular germ-cell origin, which tend to be treated in single centres. From experience with this drug we hope that its use will be encouraged in specialist centres.

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Are benign melanomas common in adults? What treatment is advised?

Most adults have moles (the term benign melanoma is neither desirable nor correct). These are naevi composed of naevocytic cells of the melanocyte series. The reasons for treatment are: (1) suspicion of malignant transformation (enlargement, darkening, bleeding, itching); and (2) cosmetic or annoyance—for instance, catching on a shirt collar or even more intimate item of clothing or anatomy. Treatment of moles is excision or shaving, depending on site, size, and nature. The small fleshy and often only slightly pigmented moles on the face are usually best treated by shaving off flush with the surface with a scalpel.