Carboplatin in Childhood Cancer

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INTRODUCTION

Carboplatin is one of a series of Platinum compounds synthesised with the aim of finding a Cisplatinum analogue with equivalent or superior anti-tumour activity but reduced renal toxicity and less emetic activity.

Cisplatinum was first used in clinical studies in the early 1970’s and is established as essential in the treatment of malignant germ cell tumours particularly teratomas. It is, however, associated with severe toxicity; in particular renal, (raised creatinine in 20% patients); peripheral neuropathy in >20%; ototoxicity in 20%, and severe nausea and vomiting which are difficult to control even with high dose antiemetic combinations. Ever since its clinical usefulness was confirmed the search has been on for a platinum compound with equivalent therapeutic efficacy but less toxicity.

MECHANISM OF ACTION OF CISPLATINUM

Cisplatinum is thought to act by inhibiting DNA synthesis. It is activated by hydrolysis with dissociation of the leaving chloride group. The reaction with DNA results in interstrand and intrastrand cross-linking and DNA protein cross-linkings. The cis transfiguration of the molecule is necessary to form a stable compound with DNA.

\[
\text{H}_2\text{N}\begin{array}{c}Cl \\
\text{Pt} \end{array}\text{H}_2\text{N} \quad \text{CISPLATINUM}
\]

This is the formula for Cisplatinum and the chloride groups are referred to as the leaving groups. It is the characteristics of the leaving groups which are thought to be critical both for toxicity and activity. Many platinum compounds have been studied and discarded but two compounds known as JM8 and JM9 were selected for further study on the basis of their activity against transplantable rodent tumors. JM8 was also active against human lung xenografts and was chosen for clinical evaluation.

CARBOPLATINUM (JM8 Paraplatin)

Chemical Structure:
diammine (1,1-cyclobutane dicarboxylate) platinum

\[
\text{H}_2\text{N}\begin{array}{c}O \\
\text{Pt} \end{array}\text{H}_2\text{N} \quad \text{PARAPLATIN}
\]

The dicarboxylate leaving group in carboplatin is more stable than that in cisplatinum leading to different characteristics compared with Cisplatinum.

Pharmacokinetics

The pharmacokinetics of carboplatin differ significantly from cisplatinum.

a) It is more stable in human plasma leading to less irreversible protein binding.
b) More carboplatin is excreted by glomerular filtration – a greater percentage of a given dose is present in the urine and hence a smaller percentage of total platinum remains in the body.
c) The terminal half life of free non-protein bound platinum is approximately ten times that of cisplatinum.
d) The terminal half life of total platinum is measurable in hours and is approximately fifteen times shorter than that of cisplatinum.

Excretion

The major route of excretion is via the kidney and total body and renal clearances of free platinum correlate with the Glomerular Filtration Rate (GFR). In man, as observed in animals, and in contrast to cisplatinum, there does not appear to be any tubular secretion. Phase I studies have indicated that toxicities correlate well with creatinine clearance and that the percentage reduction in platelet count correlates highly and linearly with the area under the curve of plasma ultrafilterable platinum. A more predictable myelosuppression is obtained by correlating the dose with GFR.

Pre-clinical studies

Pre-clinical studies of carboplatin showed activity comparable to cisplatinum in many tumour lines, superior in some and less in a few.

Clinical Studies

Phase I and II studies were done at the Royal Marsden Hospital from 1981. 69 patients were entered into a Phase I study, of whom had renal impairment. There was no evidence of nephrotoxicity or ototoxicity, nausea and vomiting were less than with cisplatinum, and the dose limiting factor was myelosuppression.

Phase III studies in adults: carboplatin has been compared with cisplatinum in a randomised study of women with ovarian carcinoma. Its reduced toxicity and equivalent therapeutic benefit was confirmed.

Dosage escalation studies in patients with stage IV ovarian carcinoma have also been done. The principal toxicities were bone marrow suppression, particularly thrombocytopenia and nausea and vomiting. No neurotoxicity was seen and alopecia was rare.

Bristol Children’s Hospital Study

From April 1986, selected patients with poor prognosis tumours or who had relapsed, were entered into the Bristol Children’s Hospital Resistant Tumour Protocol (BCH RTP) below.

| BCH RESISTANT TUMOUR-PROTOCOL I |
|----------------------------------|
| 1. Vincristine 1.5mg/sqm2 (max 2mg) weekly × 7 doses during the first cycle, than every 3 weeks. |
Table 1

| Diagnoses                  | No. of Pts. | 1st Treatment | Relapse | Previous Chemotherapy |
|----------------------------|-------------|---------------|---------|-----------------------|
| Ewing's sarcoma            | 4           | 3             | 1       | 1                     |
| Neuroblastoma              | 3*          | 2             | 1       | 1                     |
| Osteosarcoma               | 3           | 3**           | —       | —                     |
| Rhabdomyosarcoma           | 2           | 2             | —       | —                     |
| Wilm's                     | 1           | —             | 1       | 1                     |
| Sacroccygeal teratoma      | 1           | —             | 1       | 1                     |

*One inoperable ganglioneuroma.
**Had chemotherapy schedule changed because of non-response at time of biopsy.

2. Ifosfamide
MESNA 6 G/m² as a 24 hour infusion.
VP 16 150 mg/m² daily × 3.
3. Epirubicin
150 mg/m² i.v. over 15–30 minutes.
4. Carboplatin
500 mg/m² i.v. over 15–30 minutes.

Table 2 shows the time in days for nadir to be reached. It was late for the platelet count, more than half the patients actually experiencing their nadir platelet count at the time of their next chemotherapy. This led to treatment delays in 5 out of 39 courses—2 for neutropenia and 3 for thrombocytopenia.

Table 3 shows the time in days for nadir from carboplatinum treatment.

Table 2

| Nadir values following carboplatinum | Range    | Mean | Median |
|--------------------------------------|----------|------|--------|
| Total WBC × 10⁹/L                    | 0.8–10.1 | 3.9  | 3.3    |
| Neutrophils × 10⁹/L                  | 0.1–5.4  | 2.13 | 1.95   |
| Platelets × 10⁹/L                    | 40–366   | 173  | 166    |

Table 3

| Time in days to nadir from carboplatinum treatment | Range | Mean | Median |
|---------------------------------------------------|-------|------|--------|
| Total WBC                                        | 8–22  | 12   | 11     |
| Neutrophils                                      | 8–21  | 13   | 10     |
| Platelets                                        | 8–21  | 17   | 21     |

Figure 1 shows graphically the Day 0, nadir and next pre-treatment white count, neutrophil and platelet counts with the means and standard deviations.

There was only one documented case of fever and neutropenia in this group of patients following carboplatinum. Eight of the fourteen patients had long lines in situ.

b) Vomiting
All patients vomited despite receiving prophylactic antiemetics. The most common pattern was for moderate-severe vomiting to start approximately 5–6 hours after the carboplatinum and to continue for

Figure 1

Carboplatinum—Day 0, nadir and pre-treatment total WBC, neutrophil count and platelet count with means and standard deviations.
2–10 hours at home. Appetite returned to normal after approximately 36–48 hours.

c) Renal
No child who had not previously received cisplatinum had evidence of renal toxicity as measured by serial serum creatinine levels. One child, previously treated with cisplatinum to a total dose of 420 mg 3 years prior to carboplatinum, had grade I (WHO) elevation of serum creatinine at the completion of 4 cycles of carboplatinum at 300 mg/m² in December 1985. By January 1987 ⁵¹CrEDTA clearance showed his GFR to be marginally reduced. Serum magnesium has been measured after 17 courses and there has been no reduction.

d) Audiological
There was no demonstrable change in audiograms done on patients on the protocol. The child who had had previous cisplatinum therapy had bilateral high frequency loss which has remained stable since carboplatinum therapy was completed 15 months ago.

e) Liver
There was no evidence of liver toxicity as measured by changes in liver function tests such as bilirubin and aspartate transaminase.

CONCLUSIONS
Carboplatinum can be given to children at a dose of 500 mg/m², on an out-patient basis, is reasonably well tolerated (vomiting can usually be managed by parents at home) and does not cause unacceptable haematological toxicity. There was no evidence in these patients of renal, hepatic or ototoxicity. Alopecia was already present in all patients and so it is not possible for us to evaluate this though it was reported to be rare in one adult study.

REFERENCES
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