# A Short Outpatient Hydration Schedule For Cisplatin Administration

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<table>
<thead>
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Cisplatin remains a principal chemotherapy agent in the treatment of many solid tumours. However because of its nephrotoxicity, in-patient hydration schedules have been utilized to ensure safe administration.

In May 1995, due to significant load on in-patient bed availability, the Medical Oncology Department of the Cancer Therapy Centre, Liverpool Hospital, developed a short, intravenous fluid hydration protocol to be used on an out-patient setting.

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Following an initial pilot program of the abbreviated hydration regimen, a retrospective study of all adult in-patients and out-patients who received cisplatin (60-100mg/m²) from May 1995 to August 1998 was conducted.

Biochemistry was performed prior to the start of chemotherapy, and a repeat serum creatinine level was taken immediately prior to each subsequent cycle of chemotherapy, unless clinically indicated at an earlier time. The in-patient hydration protocol was 6000ml of normal saline with 60 mmol/L KCL, and 0 mmol/L MgSO₄ over 24 to 28 hours, and the out-patient hydration was 4000ml of normal saline over 6 hours.

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A total of 145 patients were included, 57 in-patient (39%) and 88 out-patients (61%), 95 males, and 50 females. The mean age was 56 years.

The maximum mean percentage change in creatinine from baseline for all cycles of chemotherapy for in-patients was 32.5% ranging from –7% to 288% (95% CI=19.9-45.11), and for outpatients 19.9% ranging from –20% to 154% (95% CI=13.47-26.39).

Although the mean increase was higher in the in-patient group by 12.6%, it was not statistically significant (p=0.079).

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In patient’s eligible for cis-platinum therapy on the basis of good performance status and normal renal function, this agent can be safely administered in the out-patient setting with an abbreviated duration, moderate volume intravenous hydration regimen.

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Cisplatin, Chemotherapy, Out-patient, In-patient, Hydration, Creatinine.

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**Introduction**

Cis-dichlorodiamine platinum (Cisplatin) has remained an invaluable chemotherapy agent for more than two decades, despite its unfavorable nephrotoxicity. Although the newer platinum compound, carboplatin is less nephrotoxic, recent studies have shown the superior anti-tumour activity of cisplatin over carboplatin in certain tumours such as squamous cell carcinomas of the upper aerodigestive tract and urogenital carcinomas (¹).

Renal impairment is well known to be the major toxicity of a single cisplatin dose of 80-100 mg/m². Lower single doses of 40-80 mg/m²

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and weekly or split administration of a larger total dose over 3-5 days have been shown to be safer in terms of acute nephrotoxicity, provided adequate hydration and urine output is maintained following the cisplatin administration (2).

Maintenance of hydration is a key element in prevention of severe cisplatin nephrotoxicity (3). However, the optimal volume and schedule of fluid to provide effective and reliable protection against acute nephrotoxicity has not been determined in a randomised trial setting.

Since the early 1990s, with the availability of more effective treatment for highly emetogenic chemotherapy regimens, selective serotonin (5-HT3) antagonists and corticosteroids, maintenance of adequate hydration via oral fluid intake following cisplatin administration has become an achievable goal in most patients. Following these developments, the out-patient administration of cisplatin has become clearly preferable to in-patient administration from a health economics and patient preference viewpoint provided it is proven to be both logistically feasible and safe.

Prior to the inauguration of the Cancer Therapy Centre in the Liverpool Health Service in May 1995, all patients requiring cisplatin had received their treatment as an in-patient.

The rapid population growth and the development of cancer services within South Western Sydney placed significant pressure on the available in-patient facilities, and therefore urged the Medical Oncology Department at Liverpool Hospital to develop a short duration, moderate volume intravenous fluid hydration regimen for use in an out-patient setting.

The aim of this study was to confirm the feasibility and the safety of cisplatin administration in the out-patient setting. The perceived potential benefits included patient convenience, improved in-patient bed utilization, and cost effectiveness.

Methods

Following a review of the published data on the experience of out-patient cisplatin administration in the USA and Europe (4-6), a pilot study was initially performed to confirm the safety of an abbreviated schedule of moderate volume hydration in patients receiving chemotherapy with cisplatin doses between 60-100mg/m².

The eligibility criteria for out-patient cisplatin administration were: (1) living within 20 km radius of Liverpool Hospital, (2) telephone at home, (3) support person available at home, (4) good performance status (Eastern Cooperative Oncology Group ECOG 0,1), and (5) normal renal function.

The criteria for in-patient cisplatin administration were (1) Age >70 years, (2) poor performance status ECOG >1), (3) potential for tumour lysis syndrome, (4) prostatic hypertrophy, (5) borderline renal function, and (6) severe nausea/vomiting from previous chemotherapy.

The hydration protocol for out-patient cisplatin administration involved the following: Normal saline 2000 ml over 2 hour, 20% mannitol 200 mls over 30 minutes, normal saline 1000 ml + cisplatin over 2 hours, normal saline 1000 ml over 1-2 hours. Provided the patient had no nausea or vomiting, the patient was discharged home.

The hydration protocol for in-patient cisplatin administration is the same as for the outpatient group except for the post cisplatin hydration as all patient will receive normal saline 3000 ml with 60 mmol/L KCl, and 30 mmol/L MgSO₄ over 20-24 hours.

The anti-emetic protocol used for both in-patients and out-patients was intravenous Ondansetron 8mg and intravenous Dexamethasone 20mg pre-chemotherapy, followed by Ondansetron 8mg orally twice daily for 3 days, and Dexamethasone 4-8mg orally daily for 3 days to reduce delayed nausea and vomiting. Pro-chlorperazine 25mg q8h by suppository was prescribed for breakthrough nausea and vomiting.

During the pilot phase of the study, 31 patients were interviewed by telephone on day 2,3 and 5 to assess anti-emetic compliance, as well as scoring common toxicity data, and overall performance status. As no significant problems arose during the pilot study, the telephone interviews were discontinued, and criteria for out-patient
administration of cisplatin were relaxed to enable the majority of patients to receive non-inpatient therapy, provided adequate support was available for them at their place of residence.

Biochemistry was performed prior to the start of chemotherapy, and a repeat serum creatinine level was taken immediately prior to each subsequent cycle of chemotherapy, unless clinically indicated at an earlier time, and at next follow up after completion of the chemotherapy.

After 3 years of implementation we conducted a retrospective review of all patients who received cisplatin (60-100mg/m²) from May 1995 to August 1998, including both in-patients and out-patients.

The statistical analysis was done using the SPSS program, with the p-value evaluated by use of a 2-tailed t-test.

Results

In the pilot study during 1995 there were 31 patients, who received 69 cycles of cisplatin. The median age was 56 years (range 26-76). On initial review of these patients we found that the hydration was well tolerated. None of the patients required admission to hospital for complications, although 2 patients were treated with intravenous fluid, and intravenous antiemetics in the Oncology clinic for delayed nausea and vomiting.

Between May 1995 and August 1998, a total of 145 patients (95 males and 50 females) received cisplatin at a dose of 60-100 mg/m², 57(39%) as in-patients, and 88(61%) as out-patients. The median age for the entire cohort was 59 years [Table 1]. A total of 454 cisplatin cycles were administered, 165 as an in-patient, and 289 as an out-patient, both with a median of three cycles.

<table>
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<tr>
<th>Table 1 : Age, Sex, ECOG type of cancer distribution for in-and out-patients</th>
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<tbody>
<tr>
<td><strong>No. Patients</strong></td>
</tr>
<tr>
<td>Mean Age</td>
</tr>
<tr>
<td>Median Age</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>SD</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
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</tr>
<tr>
<td>Female</td>
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<tr>
<td>ECOG</td>
</tr>
<tr>
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<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>Not documented</td>
</tr>
<tr>
<td>Type of cancer</td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>Gastric</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
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<tr>
<td>Oesophagus</td>
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<tr>
<td>Bladder</td>
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<tr>
<td>Gynaecological</td>
</tr>
<tr>
<td>Germ cell</td>
</tr>
<tr>
<td>Unknown Primary</td>
</tr>
<tr>
<td>Others</td>
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</tbody>
</table>
The majority of out-patients had an ECOG performance status of 0-1 (88%), while 72% of in-patients had ECOG performance status of 0-1 which was not a statistically significant difference [Table 1].

The mean baseline serum creatinine for in-patient group was 83.5 nmol/L, and for the out-patient group was 86.3 nmol/L (Fig. 1).

The maximum mean percentage change in creatinine from baseline (calculated as the maximum creatinine level minus the baseline creatinine divided by the baseline creatinine into 100) for the entire cohort was 24.9% with a median of 14%. The maximum mean percentage change in serum creatinine from baseline for all cycles of chemotherapy for in-patients was 32.5% with a median of 19% ranging from -7% to 288% (95% CI = 19.9-45.1), and for out-patients was 19.9% with a median of 11% ranging from -20% to 154% (95% CI = 13.5-26.4) which was not statistically significant (p=0.079).

The maximum mean percentage change in serum creatinine from baseline after 2 months (the creatinine level available at first visit post chemotherapy) for the whole group was available for 113 patients and was 5.1% (-30% - 179%). This reflected a change of 6.8% for 48 in-patients, and 3.9% for 65 out-patient> s p=0.64 [Table 2].

The maximum mean percentage changes in creatinine from baseline, analyzed at different cisplatin doses (60-80 mg/m² versus > 80 mg/m²), according to the in-patient and out-patient administration schedules was not statistically significant (p=0.63). [Table 2].

The mean basal serum Creatinine clearance for in-patient group was 75 ml/min and for the out-patient group was 84 ml/min. The mean lowest Creatinine clearance for in-patient group during chemotherapy was 61 ml/min and for the outpatient group was 75 ml/min. (p=0.002).

The mean basal serum Creatinine level for in-patient group was 0.82 mmol/L, and for the out-patient group was 0.8 mmol/L (range 0.5-1.25). The mean potassium level after one cycle of chemotherapy for in-patient was 0.72 mmol/L, and for the out-patient group was 0.72mmol/L.

The maximum mean percentage change in serum creatinine from baseline after 2 months (the creatinine level available at first visit post chemotherapy) for the whole group was available for 113 patients and was 5.1% (-30% - 179%). This reflected a change of 6.8% for 48 in-patients, and 3.9% for 65 out-patients p=0.64 [Table 2].

The maximum mean percentage changes in creatinine from baseline, analyzed at different cisplatin doses (60-80 mg/m² versus > 80 mg/m²), according to the in-patient and out-patient administration schedules was not statistically significant (p=0.63). [Table 2].

The mean baseline magnesium for in-patient group was 0.82 mmol/L (range 0.6-1.0), and for the out-patient group was 0.8 mmol/L. The mean magnesium level after one cycle of chemotherapy for in-patient was 0.72 mmol/L, and for the out-patient group was 0.72mmol/L.

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Table 2: Max. % change in creatinine from baseline with Cisplatin dose.

<table>
<thead>
<tr>
<th>Cisplatin dose</th>
<th>Total</th>
<th>In-patient</th>
<th>Out-patient</th>
</tr>
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<tbody>
<tr>
<td>60-80 mg/m²</td>
<td>25.6%</td>
<td>35.4%</td>
<td>18.5% p=0.63</td>
</tr>
<tr>
<td>No.</td>
<td>109</td>
<td>46</td>
<td>63</td>
</tr>
<tr>
<td>&gt;80 mg/m²</td>
<td>22.6%</td>
<td>20.4%</td>
<td>23.6% p=0.96</td>
</tr>
<tr>
<td>No.</td>
<td>36</td>
<td>11</td>
<td>25</td>
</tr>
</tbody>
</table>

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The maximum mean percentage change in serum creatinine from baseline (calculated as the maximum Creatinine level minus the baseline creatinine divided by the baseline creatinine into 100) for the entire cohort was 24.9% with a median of 14%. The maximum mean percentage change in serum creatinine from baseline for all cycles of chemotherapy for in-patients was 32.5% with a median of 19% ranging from -7% to 288% (95% CI = 19.9-45.1), and for out-patients was 19.9% with a median of 11% ranging from -20% to 154% (95% CI = 13.5-26.4) which was not statistically significant (p=0.079).

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One patient, who had initial chemotherapy as an in-patient, had further chemotherapy as an out-patient.

Discussion

Cisplatin consists of a free, non-protein bound (ultra-filterable) and a protein bound (non-filterable) components. Because the protein-bound drug is believed to lack cytotoxic activity, information regarding elimination of the unbound cisplatin appears to be of special importance. Disappearance of unbound cisplatin from plasma has a biphasic character, with an initial t½ elimination phase of 20-30 minutes and a second t½ elimination phase of one hour. Removal of plasma protein-bound platinum occurs during a prolonged terminal elimination phase that lasts several days.

The precise mechanism of cisplatin induced renal toxicity has not been clearly delineated. The mechanism of acute renal impairment associated with cisplatin administration is believed to be a pre-glomerular vasoconstriction with or without a reversible acute tubular necrosis caused by the free component of cisplatin. Kelsen and associates have shown that an increased incidence of acute nephrotoxicity is related to high peak plasma ultra-filterable cisplatin concentration. The amelioration of cisplatin nephrotoxicity by saline hydration is thought to be due to an increased renal perfusion and tubular salt and water load rather than alteration in the cisplatin pharmacokinetics. The more clearly recognized chronic renal impairment associated with cisplatin administration is due to a partially reversible, cumulative, but non-progressive, renal tubular damage. This is mainly proximal tubular damage characterized clinically by chronic renal failure, moderate reduction in glomerular filtration rate, hypokalemia, and hypomagnesemia. The clinical picture is occasionally associated with a syndrome of salt losing nephropathy characterized by symptomatic hypotension, hypovolemia associated with a deterioration in renal function, which is correctable by normal saline infusion.

Cisplatin is excreted primarily by the kidneys, and it is believed that higher urinary concentrations of the drug enhance nephrotoxicity. Therefore, the most efficient way to decrease the nephrotoxicity is to decrease the urinary concentration of cisplatin. This is accomplished by aggressive hydration before, during and after cisplatin. It appears that the first 4 hours after administration of cisplatin is a critical period during which the kidney must be protected from the toxic effects of the drug. Hays et al at the Memorial hospital in New York were among the first to show the nephroprotective effect of intravenous hydration during cisplatin administration. Legha et al at the M.D. Anderson Cancer Center confirmed that hydration reduces the risk and severity of cisplatin-associated renal damage. Accordingly, in-patient administration of cisplatin at the relatively large single dose of 100 mg/m² in conjunction with moderate to large volume intravenous hydration became the standard way of cisplatin administration in mid 1980’s.

Along with the better understanding of the risk factors for the development of cisplatin nephrotoxicity (such as advanced age, poor performance status, background renal impairment, low intravascular volume, low cardiac output states, and poor fluid intake) clinicians became gradually more confident to select low risk patients for out-patient treatment. The advent of 5-HT3 antagonists in early 1990’s produced better control of nausea and vomiting. This facilitated maintenance of adequate oral hydration has also encouraged Oncologists to shift cisplatin administration to the out-patient setting.

Considering the volume of hydration as the main difference between the out-patient and in-patient administration of cisplatin, there are some recent, though scarce data to support the safety of lower volume hydration. Stewart et al retrospectively assessed factors associated with cisplatin nephrotoxicity in 425 patients treated with cisplatin at the Ottawa Regional Cancer Centre between 1982 and 1992. All patients were treated in the era prior to the availability of 5-HT3 antagonist anti-emetics. In this non-randomized study the relationship between the total cumulative dose of cisplatin and residual nephrotoxicity after completion of cisplatin...
therapy (on the basis of pre-chemotherapy and end of chemotherapy serum creatinine difference) was evaluated. Multivariate analysis showed no difference in degree of nephrotoxicity between patients receiving lower or higher hydration volumes.

Of importance, the hydration regimen during cisplatin administration appears to ameliorate only acute cisplatin induced renal damage, having a modest impact on chronic renal impairment. Cumulative chronic renal impairment, which is a function of total dose of cisplatin administration in an individual patient, can only be effectively modulated by administration of potent cytoprotectors such as amifostine rather than vigorous hydration (11).

Although not statistically significant, our study demonstrates a trend towards less nephrotoxicity in the outpatient cisplatin group. As the out-patient group received a lower overall fluid volume, it is postulated that the rate of post platinum hydration (i.e. large volume of fluid over a short time period) may therefore provide some protection against nephrotoxicity.

Although initially it was thought that particular selection criteria might need to be applied in choosing patients for “out-patient” administration, relaxation of the selection criteria did not appear to increase the risk of adverse events. In selecting patients for out-patient chemotherapy, certain general guidelines should be followed. The patients should be well nourished, with a good performance status, and free of significant cardiopulmonary or renal disease.

The benefits of this approach have included patient convenience, the ability to deliver chemotherapy in a timely manner with no delays and improved in-patient bed utilization.

Additional research to determine the optimum volume, and rate of hydration required to prevent cisplatin induced nephrotoxicity is needed.

In this retrospective study we have confirmed both the feasibility and safety of a moderate volume hydration schedule when compared with a conventional schedule. This study also confirms a role for the non-inpatient administration of cisplatin, which has substantive implications in term of reducing health care costs. Importantly this can be achieved without increasing the risk of platinum induced nephrotoxicity.

**Conclusion**

Cisplatin can be safely administered in the out-patient setting with an abbreviated duration, moderate volume intravenous hydration regimen. Patients with normal renal function and good performance status may be considered to have cisplatin as an out-patient.

**Acknowledgment**

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