Original Article

Cumulative prior dose of cisplatin as a cause of the nephrotoxicity of high-dose chemotherapy followed by autologous stem-cell transplantation

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Abstract

Background. Nephrotoxicity is one of the most frequent dose-limiting factors of high-dose chemotherapy to create tolerance of autologous peripheral blood stem-cell transplantation (PBSCT) for the treatment of malignant diseases. The relative importance of factors that may be responsible for the development of nephrotoxicity varied in different trials.

Methods. The factors affecting nephrotoxicity in the early period of high-dose ifosfamide, carboplatin and etoposide treatment (ICE) followed by autologous PBSCT was investigated in 47 patients. ICE was given as a conditioning regimen for 6 days. Nephrotoxicity was defined as an increase in the serum creatinine concentration of 0.5 mg dl⁻¹ or more over individual baseline levels.

Results. Eleven patients developed nephrotoxicity (23.4%). There was no significant difference in baseline renal function between patients with nephrotoxicity and those without. No differences were found between the two groups in terms of average total doses of ICE, infections and antibiotic use. The age of patients was higher in those with nephrotoxicity (37 ± 3.7 vs 26 ± 1.7 years, P = 0.019). The cumulative cisplatin dose administered prior to this regimen was higher in the group that developed nephrotoxicity (470 ± 227 mg m⁻², P = 0.02). The overall mortality rate was 17%, but the transplant-related deaths were higher in the presence of nephrotoxicity (54.5 vs 5.5%, P = 0.001).

Conclusions. The cumulative dose of cisplatin is a strong risk factor for the development of nephrotoxicity in patients who receive high doses of ICE followed by PBSCT. Nephrotoxicity may occur with much lower doses than the currently recommended maximum doses.

Keywords: antineoplastic agent toxicity; autologous bone-marrow transplantation; high-dose chemotherapy; nephrotoxicity

Introduction

Combined therapy with high-dose ifosfamide, carboplatin and etoposide followed by autologous peripheral blood stem-cell transplantation (ICE/PBSCT) has been used with increasing response rates for the treatment of several malignancies [1–4]. Nephrotoxicity is a well-recognized side-effect of this treatment. It could be related to multiple factors including medications, patient characteristics and co-morbidities. The relative importance of these factors in the development of nephrotoxicity has not been delineated conclusively.

Earlier studies suggest that the strongest risk factors for the development of renal insufficiency in patients undergoing bone-marrow transplantation are hepatic dysfunction, amphotericin B usage and septicemia [5]. A more recent study proposed that early renal dysfunction might be attributable to the high dose of ifosfamide in patients receiving ICE therapy [6]. Previous exposure to cisplatin in patients receiving ICE/PBSCT is another potential cause. There are, however, conflicting studies of this idea [7,8].

The specific aim of this study was to analyse our patient cohort, who received ICE/PBSCT over a period of 30 months, in terms of nephrotoxicity and other possible associated factors.

Subjects and methods

Patients

Forty-seven consecutive patients who underwent high-dose ICE treatment followed by autologous PBSCT in our...
bone-marrow transplantation centre between August 1996 and February 1999 were enrolled in this analysis. The study had a prospective, observational design. The characteristics of patients are shown in Table 1. The most common diagnoses were breast cancer and osteosarcoma.

Pre-treatment evaluation

Prior to the administration of ICE/PBSCT, pulmonary function tests, left ventricular ejection fraction by two-dimensional echocardiography, chest X-ray, and a comprehensive metabolic panel were carried out in all patients. Each patient’s creatinine clearance was calculated according to Cockroft–Gault (C–G) formula before ICE/PBSCT. Glomerular filtration rate (GFR) was calculated according to the simplified version of the Modification of Diet in Renal Disease (MDRD) Study prediction equation formula: $\text{GFR} = 186 \times \text{Pcr}^{1.154} \times \text{Age}^{-0.203} \times 0.742$ (if black) $\times 0.742$ (if female) defined by Levey [9]. In addition, the total cumulative cisplatin dose (mg/m²) administered prior to ICE/PBSCT was calculated.

Collection of peripheral blood stem cells and high-dose therapy

The treatment protocol is shown in Figure 1. In brief, 14 days after the last induction day of chemotherapy, the stem cells were mobilized by a haematopoietic growth factor (granulocyte-colony-stimulating factor, G-CSF, 10–15 µg/kg/day). Within 4–6 days after G-CSF, leukapheresis was performed using the Cobe aphaeresis system (Cobe Spectra, Cobe Lakewood, CO, USA). Dimethylsulphoxide was added to the harvest, which was then frozen to $-100^\circ$C. Two days after the completion of therapy, the harvest was thawed and infused via a centrally placed venous catheter. The chemotherapy regimen consisted of high-dose ICE. Throughout the 2½ years of the study, there was no predetermined ICE dose because of different clinical protocols. The high-dose treatment regimen consisted of total doses of 7900–15 200 mg/m² of ifosfamide, 700–1520 mg/m² of carboplatin, and 700–1550 mg/m² of etoposide. Each cytostatic drug was administered in six divided doses from days to as a 3 h infusion. MESNA, which was used as a uroprotectant, was given on days to by 24 h continuous infusion. ICE regimen was accompanied by vigorous alkaline diuresis. All patients received hydration with 5% dextrose and normal saline at 200 ml/h. Sodium bicarbonate (44–88 mEq/l) and potassium chloride were given as needed. All patients received 300 mg/day of allopurinol p.o. during this period.

Post-transplant supportive care

Each patient was isolated in a room equipped with ultraviolet lamps. They received vigorous intravenous hydration and total parenteral nutrition. If neutropenic fever occurred, broad-spectrum antibiotic therapy was initiated. Ceftazidime or imipenem together with amikacin were used for this purpose. Amikacin was used as a single dose of 15 mg/kg/day. Aminoglycoside antibiotic therapy was not given in the 8 weeks prior to PBSCT. These antibiotics were modified according to culture and sensitivity results. Throughout the treatment period, serum potassium, bicarbonate and calcium concentrations were monitored daily and replacement therapy was initiated as needed. Patients’ body weight as well as fluid input and output were assessed daily. Patients were discharged from hospital when their platelet count was above $20 \times 10^9$/l without transfusion, and their neutrophil...
count was > 500 μl, without apparent signs of infection and with adequate oral intake.

**Evaluation of nephrotoxicity**

Serum urea and creatinine were drawn daily. Urinary sodium levels were assessed when nephrotoxicity was detected. For the purposes of this study, renal failure (nephrotoxicity) was defined as an increase in the serum creatinine concentration of 0.5 mg/dl or more, over individual baseline levels. This reflected a mean drop of 56% (31.4–80%) in the GFR estimated with the prediction equation formula for this patient population.

**Statistical analysis**

The Shapiro–Wilks test was used to determine normal distribution within groups. Comparisons were carried out by non-parametric methods. The results are reported as median and standard error (SE).

In both groups, the Mann–Whitney U-test was used to compare values such as drug doses, age, serum creatinine and creatinine clearance. The χ² and median tests were used to compare some other variables such as prior cisplatin use, positive blood cultures or causes of sepsicaemia. Fisher’s exact correction was used when appropriate. For variables with non-parametric distribution, logistic models were established to evaluate the effect of total prior cisplatin dose. Spearman correlation analysis was used for simple correlations.

**Results**

**Nephrotoxicity**

Eleven patients (23.4%) met our criteria for nephrotoxicity. All nephrotoxic patients had urinary sodium levels >40 mEq/l when nephrotoxicity was detected. In this group, the increase in serum creatinine concentration was >1 mg/dl in eight patients and 0.5–1 mg/dl in three patients. Five patients required haemodialysis. One patient’s renal malfunction resolved after eight haemodialysis sessions and the patient was discharged on the 36th post-transplantation day.

**Table 2. Characteristics of the patients**

<table>
<thead>
<tr>
<th></th>
<th>Patients with nephrotoxicity</th>
<th>Patients without nephrotoxicity</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>11 (23.4%)</td>
<td>36 (76.6%)</td>
<td></td>
</tr>
<tr>
<td>M/F ratio</td>
<td>6:5</td>
<td>18:18</td>
<td>NS</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>5 (45.4%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>37.0 ± 3.7 (23–67)</td>
<td>26.0 ± 1.7 (15–51)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)*</td>
<td>1.0 ± 0.06 (0.6–1.3)</td>
<td>0.8 ± 0.03 (0.5–1.2)</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)*</td>
<td>104.0 ± 9.68 (51–152)</td>
<td>108.0 ± 4.14 (60–170)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>6 (54.5%)</td>
<td>2 (5.5%)</td>
<td></td>
</tr>
<tr>
<td>Pre-ICE Cisplatin use (n)</td>
<td>6 (54.5%)</td>
<td>22 (61.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Total cisplatin dose (mg/m²)</td>
<td>470 ± 108 (290–975)</td>
<td>227 ± 49 (170–950)</td>
<td></td>
</tr>
<tr>
<td>ICE (mg/m²)</td>
<td>11 750 ± 590 (7900–15 150)</td>
<td>11 800 ± 212 (9300–15 200)</td>
<td>NS</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>1175 ± 70 (700–1515)</td>
<td>1197 ± 20 (780–1520)</td>
<td>NS</td>
</tr>
<tr>
<td>Etoposide</td>
<td>1175 ± 79 (700–1515)</td>
<td>1200 ± 24 (980–1520)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*aAt baseline. *bCreatinine clearance calculated with the Cockroft–Gault formula. *cGFR calculated with the simplified MDRD Study prediction equation formula. NS = Not significant.

In this group, the increase in serum creatinine concentration was >1 mg/dl in eight patients and 0.5–1 mg/dl in three patients. Five patients required haemodialysis. One patient’s renal malfunction resolved after eight haemodialysis sessions and the patient was discharged on the 36th post-transplantation day.

Table 2 shows the characteristics of patients, comparing those with and those without nephrotoxicity. There was no significant difference in baseline renal function between the two groups.

The decline of renal function in patients with nephrotoxicity occurred during the high-dose therapy or shortly thereafter. Among five patients who required haemodialysis, two experienced nephrotoxicity 4 days prior to stem-cell reinfusion (day –4), and the others on day –2, day 0 and day +1 respectively. Among six patients who did not require haemodialysis, three experienced nephrotoxicity on the day of reinfusion (day 0) and the others on days +2, +4 and +6 respectively.

No significant correlations were identified between the primary diagnoses of the patients and nephrotoxicity.

**The effect of drug therapy**

**ICE therapy.** There was no significant difference between the two groups for average total doses of ICE (Table 2).

**Previous cisplatin use.** Twenty-eight patients had received cisplatin before the ICE/PBSCT regimen. Cisplatin use was not significantly different between the two groups (P = 0.74). However, in patients who developed nephrotoxicity the cumulative cisplatin dose administered prior to ICE/PBSCT was significantly higher.

The median value of the total cisplatin dose used prior to high-dose ICE therapy for all patients was

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282.5 mg/m². In order to evaluate the risk of nephrotoxicity, we compared the incidence of nephrotoxicity in patients who had received prior cisplatin doses higher than the median value vs patients who had received prior cisplatin doses lower than the median value. Indeed, all patients in the group with nephrotoxicity had received cisplatin doses higher than the median value, and 42.8% of patients who received cisplatin doses higher than this value developed nephrotoxicity.

**Infections.** Thirty patients had positive blood cultures with 41 organisms. Twelve micro-organisms were detected in eight of the patients with nephrotoxicity (73%) and 29 micro-organisms were detected in 22 patients without nephrotoxicity (61%). Overall, the most common bacterium was *Staphylococcus aureus* (48.78%). There was no difference between the two groups in terms of bacterial isolation ($P = 0.08$) and isolated bacterial types ($P = 0.66$).

**Antibiotic use.** Of the 11 patients with nephrotoxicity, nine were treated empirically with antibiotics. Nephrotoxicity occurred in five of them (55.5%) before the use of any antibiotics. In four patients, the drug was introduced before the increases in their serum creatinine concentrations, and these patients developed this complication just 1, 2 and 3 days after starting aminoglycoside therapy. Similar empirical antibiotic therapy (ceftazidime or imipenem together with amikacin) was used in all of the patients in the group without nephrotoxicity. There was no significant difference between the two groups in the use of antibiotics.

**Age.** The age of patients who developed nephrotoxicity was significantly higher (Table 2).

**Other toxicities.** Haematological and gastrointestinal system (GIS) toxicities were graded according to WHO criteria. The bone-marrow-depressing effect of ICE therapy was observed in all patients. No difference was found between the two groups in terms of haematological system toxicity. The incidence of GIS toxicity was about the same in both groups (64% in the group with nephrotoxicity and 69% in the group without). However, the degree of hyperbilirubinaemia was higher in the nephrotoxicity group ($\chi^2 = 11.57, P = 0.02$).

**Mortality.** Short-term mortality in this small patient cohort was 17% (8/47). Five patients died from multi-organ failure including renal failure, two patients died from sepsis (*Candida* and *Staphylococcus aureus*) and one patient died from adult respiratory distress syndrome. Mortality in this population is known to be increased with nephrotoxicity (54.5% vs 5.55% in those without nephrotoxicity, $P = 0.001$) especially among those requiring haemodialysis, who have mortality rates of 80%.

**Discussion**

Nephrotoxicity is one of the most significant complications of ICE/PBSCT treatment [2,4,10–12]. The incidence of nephrotoxicity has been reported as 29 and 48% in two previous studies [6,8]. In our study the incidence was 23.4%, and we found that the cumulative dose of cisplatin administered prior to ICE-PBSCT therapy was an important determining factor.

Several studies have reviewed the factors that could predispose to development of nephrotoxicity during the ICE/PBSCT regimen. These include patient characteristics, underlying malignant disease, the development and severity of post-transplant hepatic failure, pre-transplant renal function and concomitant use of nephrotoxic agents [2,5,13,14]. In addition, the chemotherapeutic agents in this protocol are capable of causing nephrotoxicity [13,15].

According to the dose-escalating studies, the maximum total doses recommended for ifosfamide, carboplatin and etoposide in combined therapy are: 10 000–20 100 mg/m², 1350–2000 mg/m², and 1200–3000 mg/m² respectively [2,4,10,12]. Nephrotoxicity was observed more frequently when these doses were exceeded. In our study, nephrotoxicity was observed in patients who received much lower doses than these. Furthermore, the average total doses were comparable between the two groups. Therefore it is unlikely that any one of the study drugs is solely responsible.

A significant factor predictive of the development of nephrotoxicity in our patients was previous use of cisplatin. All patients who developed nephrotoxicity had received cisplatin in doses exceeding the median cisplatin dose of 282.5 mg/m². Consistent with our results, Goren et al. [16] reported that if the previous total cisplatin dose was higher than 360 mg/m², the risk of nephrotoxicity increased in patients undergoing subsequent chemotherapy.

The occurrence of nephrotoxicity early during the high-dose ICE protocol and PBSCT, along with the absence of any differences between the groups with regard to infections and antibiotic use and the high urinary sodium levels in patients with nephrotoxicity, lead to the conclusion that the development of renal deterioration was primarily related to the chemotherapy.

In this study, the increase in serum creatinine concentration of 0.5 mg/dl or more over the baseline concentration was taken as the indicator of nephrotoxicity [17,18]. Several groups have also selected this criterion as a cut-off level for discontinuation of the chemotherapy [2,8].

Although infections and the use of nephrotoxic antibiotics are known to be important risk factors for the development of nephrotoxicity, we were unable to detect any differences between the two groups in terms of micro-organisms isolated, isolated bacterial types, the incidence and severity of sepsis, or specific antibiotics. Indeed, identical antibiotic protocols were used in both groups of patients. Two nephrotoxic patients did not receive antibiotics. Of those in the nephrotoxic
group who required antibiotics, 55.5% had increased serum creatinine levels > 0.5 mg/dl before any antibiotics were given. Although four patients had been receiving aminoglycosides before the increases in their serum creatinines, the occurrence of nephrotoxicity within a few days of starting aminoglycosides suggests that antibiotics may not be the only culprits in the development of nephrotoxicity. Similarly, Rossi et al. [19] reported that gentamicin had no influence on renal functions in patients undergoing ifosfamide therapy. Nevertheless, the increased risk of aminoglycoside nephrotoxicity during bacteremia may be a factor contributing to nephrotoxicity in some patients.

Consistent with an earlier report [11], our study showed that patients who developed nephrotoxicity tend to be slightly older. Although both groups were young, this result suggests that the age of patients should be taken into account when scheduling ICE/PBSCT.

In summary, the cumulative prior dose of cisplatin is a strong risk factor for the development of nephrotoxicity in patients undergoing high-dose ICE followed by PBSCT. Nephrotoxicity may occur with much lower doses of chemotherapeutic agents than the recommended maximum doses. Once nephrotoxicity occurs, the mortality rate is very high, especially in patients who require hemodialysis for the treatment of acute renal failure. Therefore we recommend that cisplatin use should be reduced and the cumulative dose be limited to less than 300 mg/m² in order to minimize the risk of nephrotoxicity during ICE/PBSCT.

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References


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