

Acute renal toxicity of 2 conditioning regimens in patients undergoing autologous peripheral blood stem-cell transplantation

Total body irradiation-cyclophosphamide versus ifosfamide, carboplatin, etoposide

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ABSTRACT

الأهداف: مقارنة التسمم الكلوي الحاد لنظامين علاجيين معدلين بالإشعاع الكامل للجسم/ ساكلوفوسفاميد (TBI-Cy) وآيفوسفاميد و كاربوبلاتين وإيتوبوسيد (ICE).

الطريقة: تمت معالجة المرضى في الفترة ما بين أغسطس 1996م و فبراير 2004م، بزراعة الخلايا الجذعية الدموية المحيطية الذاتية بقسم الأورام والعلاج الإشعاعي بمدرسة غولهان الطبية العسكرية بأنقرة - تركيا، بنظامين علاجيين مختلفين معدلين. وتم تحليلهما بالمقارنة، من أجل التسمم الكلوي الحاد في الفترة المبكرة عقب عملية الزراعة. تلقى 47 مريضاً النظام العلاجي (ICE) بمقدار 1.2 g/m²; 1.2 g/m²; 12 g/m² على التوالي وتم تقسيمهم إلى ستة أيام متتالية، بينما تلقى 21 مريضاً (6 جرعات من TBI Gy، مرتين يومياً، لمدة ثلاثة أيام متتالية)، و (60mg/m²) في اليوم من ساكلوفوسفاميد لمدة يومين.

النتائج: تم تقييم حالة 68 مريضاً في هذه الدراسة. لم يكن هنالك اختلافاً ملحوظاً في الخط القاعدي لوظيفة الكلى بين المرضى في مجموعة (ICE) ومجموعة (TBI-Cy). تعرض 11 مريضاً لتسمم كلوي (23.4%) في مجموعة (ICE)، بينما تعرض مريضاً واحداً للتسمم الكلوي (4.8%) في مجموعة (TBI-Cy) ($p=0.06$). خمسة مرضى من 11 مريضاً أصيبوا بتسمم كلوي في مجموعة (ICE) مما تطلب إجراء التنقية الدموية لهم وتوفي أربعة منهم (8.5%). في المقابل توفي مريضاً واحداً (4.8%) نتيجة للتسمم الكلوي على الرغم من التنقية الدموية في مجموعة (TBI-Cy).

الخاتمة: تكشف هذه الدراسة أن نظام (TBI-Cy) العلاجي المعدل، لا يبدو أقل سمية من نظام (ICE) خاصة لدى المرضى الذين استعملوا سيسبلاتين قبل الزراعة.

Objective: To compare acute renal toxicity of 2 conditioning regimens of total body irradiation/cyclophosphamide (TBI-Cy) and Ifosfamide, Carboplatin, and Etoposide (ICE).

Methods: Between August 1996 and February 2004, patients treated with autologous peripheral stem cell transplantation in the Department of Medical and Radiation Oncology, Gulhane Military Medical School, Ankara, Turkey with 2 different conditioning regimens was comparatively analyzed for acute renal toxicity in the early post-transplant period. Forty-seven patients received ICE regimen with 12 g/m²; 1.2 g/m²; and 1.2 g/m² divided to 6 consecutive days, whereas 21 patients received 12 Gy TBI (6 fractions twice daily in 3 consecutive days) and 60 mg/m²/day cyclophosphamide for 2 days.

Results: Sixty-eight patients were evaluated in this study. There was no significant difference in baseline renal function between patients in the ICE and TBI-Cy groups. Eleven patients developed nephrotoxicity (23.4%) in the ICE group while one patient (4.8%) in the TBI-Cy group developed nephrotoxicity ($p=0.06$). Five out of 11 patients developing nephrotoxicity in ICE group required hemodialysis and subsequently 4 (8.5%) of them died. In contrast, one patient (4.8%) died due to nephrotoxicity despite hemodialysis in the TBI-Cy arm.

Conclusion: This study reveals that the TBI-Cy conditioning regimen seems no more nephrotoxic than an ICE regimen particularly in patients who had used cisplatin prior to transplantation.

Saudi Med J 2008; Vol. 29 (6): 832-836

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Received 16th November 2007. Accepted 14th April 2008.

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Autologous peripheral blood stem-cell transplantation (APBSCT) after high-dose chemotherapy and total-body irradiation (TBI) is a widely accepted approach in the management of several malignant diseases. However, few reports exist on the renal consequences of APBSCT conditioning with TBI, but all consistently notify on the potential toxicity that ultimately leads to renal failure.¹⁻³ Total-body irradiation is usually preceded by cytotoxic chemotherapy due to the toxicity of the high TBI doses that is required to immunosuppressant adequately for donor marrow engraftment. Most commonly, cyclophosphamide (Cy), has been used either before or after TBI in order to potentiate the effects of radiation. The renal effects of Cy in combination with TBI are not well known. Nephrotoxicity is also one of the most common dose-limiting causes of intensive chemotherapy in APBSCT for the treatment of malignant diseases. Combined therapy with high-dose ifosfamide, carboplatin, and etoposide (ICE) followed by APBSCT has been used for the treatment of several malignancies.⁴⁻⁷ Nephrotoxicity is a well recognized side-effect of this treatment.^{8,9} Renal toxicity after APBSCT can also be related to a number of different agents, such as conditioning chemotherapy, post-transplant antibiotics, prior cisplatin use, infections and co-morbid diseases.^{5,10-14} The relative importance of these factors in the development of nephrotoxicity has not been delineated conclusively. Nevertheless, both conditioning TBI-Cy and ICE regimens may play a role in the pathogenesis of this serious complication. In the light of these data, we aimed to compare acute renal toxicity of 2 conditioning regimens of total body irradiation/cyclophosphamide (TBI-Cy) and ICE regimen in this study.

Methods. Between August 1996 and February 2004, 68 patients treated with APBSCT at our center with 2 different conditioning regimens were retrospectively analyzed for renal toxicity in the early (6 months) post-transplant period. All patients undergoing APBSCT were included in this study provided that they received either TBI-Cy or ICE as a conditioning regimen. Written informed consent was obtained from all patients. Prior to the administration of either TBI-Cy or ICE regimens, pulmonary function tests, left ventricular ejection fraction by 2-dimensional echocardiography, chest x-ray, and a comprehensive metabolic panel were carried out in all patients. Serum urea and creatinine were collected daily. Urinary sodium levels were assessed when nephrotoxicity was detected. Each patient's creatinine clearance was calculated according to Cockcroft-Gault (C-G) formula. Nephrotoxicity was defined as an increase in the serum creatinine concentration of ≥ 0.5 mg/dl over individual baseline level. Twelve patients

met our criteria for nephrotoxicity. Twenty-one patients received TBI the day after completion of high-dose Cy (60 mg/m²/day for 2 consecutive days). The details of our TBI technique were reported in previous studies.^{15,16} Total-body irradiation was delivered in 6 equally divided fractions over 3 days, twice a day (8-hour minimum interval between fractions, with a dose rate of 0.02-0.04 Gy/min) with Cobalt-60 teletherapy machine in all cases. The dose prescribed to the central axis (abdomen) was 12 Gy 12 Gy (6 x 2.00 Gy) for all patients. The target volume of TBI was the entire body, fitting the whole body into the diagonal size of 174.5-195 cm. The length of the body was fitted to 1.62 meter (85% isodose). The patients laid supine with legs bent on a mobile couch, which has motorized vertical movement. The head and neck supported, and partially immobilized by a comfortable molded head-base placed between the rigidly mounted compensators. Partial lung shielding was established by the patients' own arms. The kidneys and the liver were never shielded. In vivo dosimetry was performed during the first treatment session, using either thermoluminescence dosimeters (TLD) placed on the central axis and off-axis (head-front, neck, mediastinum, bilateral chest, thigh, and leg) anatomic sites. Forty-seven patients received ICE regimen with a total dosage of 12 g/m²; 1.2 g/m²; and 1.2 g/m² divided to 6 consecutive days. The application scheme of ICE regimen was reported previously.¹⁴ Thus, mesna, allopurinol, and hydration with 5% dextrose and normal saline were given to all patients. Serum urea and creatinine levels were measured daily, whereas urinary sodium levels were evaluated only in cases of nephrotoxicity. An increase in the serum creatinine concentration of ≥ 0.5 mg/dl over individual baseline levels was defined nephrotoxicity.

Mann-Whitney U-test was performed to compare drug doses, age, serum creatinine and creatinine clearance. The Chi-square and Fisher's exact correction tests were used to compare the prior cisplatin use, positive blood cultures and bacterial types, the incidence of nephrotoxicity, hemodialysis, and mortality rates due to renal toxicity. All statistical tests were 2-sided with a probability value of 0.05 considered significant.

Results. The characteristics of patients were summarized in **Table 1**. The median age of patients in both groups was similar. There was no significant difference in baseline renal function between the 2 groups. All nephrotoxic patients had urinary sodium levels >40 mEq/L when nephrotoxicity was detected. Eleven patients developed nephrotoxicity out of 47 (23.4%) in the ICE group while one patient out of 21 (4.8%) in the TBI-Cy group developed nephrotoxicity ($p=0.06$) (**Figure 1**). In ICE group, the increase in serum

creatinine concentration was >1 mg/dl in 8 patients and 0.5–1 mg/dl in 3 patients. Five patients required hemodialysis. One patient's renal malfunction was resolved after the 8th hemodialysis sessions, and the patient was discharged on the 36th post-transplantation day. Short-term mortality due to renal failure in this small cohort patient was 7% (5/68). Four patients (8.5%) died in ICE group, while one patient (4.8%) died in TBI-Cy group due to nephrotoxicity ($p>0.05$). The autopsy was performed to one patient who died of acute renal toxicity after ICE regimen. Histopathological examination of both kidneys revealed that there were fragments of cells within the tubular lumina, the flattening of the tubular epithelium, and the loss of nuclei, typical findings of acute tubular necrosis (Figure 1). The number of patients receiving cisplatin prior to ICE, and TBI-Cy regimens were 28 (60%) and 21 (100%). The used of Cisplatin was not significantly different between the 2 groups ($p>0.05$). However, the median cumulative cisplatin dose administered prior to ICE/APBSCT was significantly higher than TBI-Cy conditioning regimen (348.5 mg/m² versus 250 mg/m², $p<0.05$). Thirty patients (64%) had positive blood cultures in ICE and TBI-Cy groups. Overall, the most common bacterium was *Staphylococcus aureus* (52%). There was no difference between the 2 groups in terms of bacterial isolation ($p=0.91$) and isolated bacterial types ($p=0.74$). Of the 12 patients with nephrotoxicity, 10 were treated empirically with antibiotics. Nephrotoxicity occurred in 6 (50%) before the use of any antibiotics. No significant

difference was found between the 2 groups in terms of antibiotics usage. World Health Organization (WHO) criteria were used for the evaluation of hematological and gastrointestinal toxicities.¹⁷ No difference was found between the ICE and TBI-Cy arms in terms of hematological system toxicity. The incidence of gastrointestinal toxicity was approximately the same in

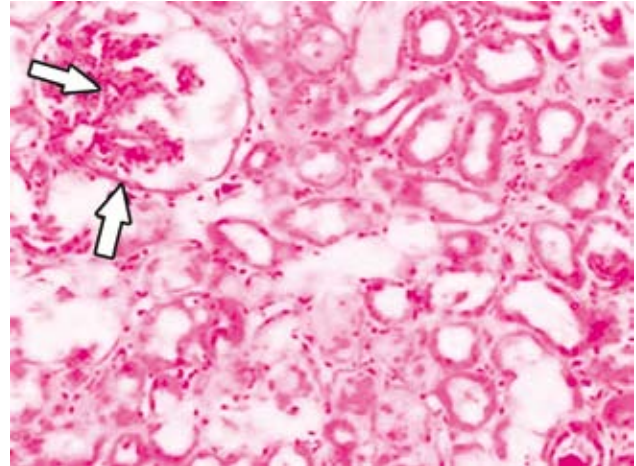


Figure 1 - Histopathological examination of the kidney tissue of the patient who died due to acute renal toxicity after receiving Ifosfamide, Carboplatin and etoposide regimen. There are fragments of cells within the tubular lumina, the flattening of the tubular epithelium, and the loss of nuclei, which are typical findings of acute tubular necrosis (Hematoxyline & Eosine X100).

Table 1 - Demographic characteristics of the patients.

Clinical features	ICE	TBI-Cy	P value
	N=47 median (range)	N=21 median (range)	
Age (years)	31	24	NS
Serum creatinine (mg/dL)	0.87 (0.50-1.30)	0.74 (0.6-1.3)	NS
Creatinine clearance (mL/min)*	108.4 (51-170)	112.2 (75-165)	NS
Pre-transplant cisplatin dosage (mg/m ²)	348.5 (170-975)	250.00 (200-400)	<0.05

ICE - Ifosfamide, Carboplatin, etoposide; TBI-Cy - total body irradiation-cyclophosphamide, *creatinine clearance calculated with the Cockcroft-Gault formula.

Table 2 - Acute renal toxicity and mortality rates of TBI-Cy and ICE groups (N=68).

Toxicity and mortality rates	ICE	TBI-Cy	P value
	N=47	N=21	
Acute renal toxicity (%)	11 (23.4)	1 (4.8)	p=0.06
Hemodialysis (%)	5 (10.6)	1 (4.8)	NS
Death due to renal toxicity (%)	4 (8.5)	1 (4.8)	NS

ICE - Ifosfamide, Carboplatin, Etoposide; TBI-Cy - total body irradiation-cyclophosphamide, NS - not significant

both groups (67% in the ICE group and 71% in the TBI-Cy group).

Discussion. We compared acute renal toxicity of the 2 conditioning regimens and found that TBI-Cy had a trend toward less nephrotoxicity than ICE regimen (4.8% versus 23.4%, $p=0.06$). One of our concern is that using the upper limit of normality for serum creatinine level as the end point may underestimate the renal toxicity. However, several groups have also selected this criterion as a cut-off level for discontinuation of the chemotherapy.^{5,9} Furthermore, several trials have demonstrated that a decrease in glomerular filtration rate is almost always associated with an increase in serum creatinine in young patients.^{11,13,18} Since the median age for ICE was 31 years and 24 years in TBI-Cy groups, serum creatinine levels can be considered to be a suitable parameter of renal failure. It can be argued that an analysis in the early (6 months) post-transplant period is too short to observe the true incidence of renal toxicity. However, the median time to renal impairment after TBI was reported to be earlier than 6 months when creatinine level was taken as the indicator of renal impairment.¹⁹ Delgado et al¹⁹ reported that the median time to renal impairment was 3 months in 241 patients receiving TBI-based preparative regimens for allogeneic hematopoietic cell transplantation. Similarly, Miralbell et al²⁰ demonstrated that the impairment of renal function tests might occur as early as 4 months in patients undergoing TBI and BMT. Therefore, we think that our follow-up period seems to be adequate to document in terms of renal toxicity. Several reports have suggested a potential role of TBI in the development of renal failure after bone marrow transplantation.¹⁻³ Miralbell et al¹ showed that the 18 months probabilities of having a normal serum creatinine level were 95% and 74% for patients conditioned with 10 Gy and 12 Gy fractionated TBI regimen. It has also previously been shown that the incidence of renal damage is closely related with TBI dose-fractionation patterns.^{1,3} In current study, we used a total dose of 12 Gy delivered in 6 equally divided fractions over 3 days, and the incidence of nephrotoxicity is similar to the previous reports using the identical TBI schedule. We observed acute renal toxicity in one patient (4.8%) in the TBI-Cy arm, and he died despite hemodialysis. Nephrotoxicity is also one of the most significant complications of ICE treatment.⁴⁻⁷ The incidence of renal toxicity in current series was 23% in patients receiving ICE, which is comparable with previous series. Several studies have evaluated the factors that could predispose to development of nephrotoxicity during the ICE regimen.¹²⁻¹⁴ We performed an in-depth analysis of the role of cisplatin and reported that the

cumulative dose of cisplatin administered prior to ICE therapy was an important determining factor for nephrotoxicity.¹⁴ In current series, patients in the ICE groups were quite heterogeneous in relation to their diagnosis and received also higher cumulative doses of cisplatin during the treatment of their primary cancers. Therefore, previous cisplatin use with high cumulative doses might enhance the renal toxicity of ICE regimen. However, cisplatin-induced renal failure is associated with increased serum creatinine and decrease creatinine clearance; and nephrotoxicity typically appears during the second week after administration of the drug. Furthermore, renal impairment is usually reversible and the recovery generally occurs within 2-4 weeks. In our current series, the mean basal serum creatinine levels and creatinine clearances were similar in both groups prior to BMT, suggesting that the renal functions of patients were comparable before administration of 2 conditioning regimens. In the current study, it is also noteworthy that 60% of patients in ICE and all patients in TBI-Cy group had a prior history of used of cisplatin. In this aspect, TBI-Cy seems to be a safe conditioning regimen for patients receiving cisplatin prior to BMT as long as the doses are lower as in our study. Although infections and the use of nephrotoxic antibiotics are known to be important risk factors for the development of nephrotoxicity, we did not detect any differences between the patients receiving ICE and TBI-Cy regimens in terms of micro-organisms isolated, isolated bacterial types, the incidence of infections, or specific antibiotics. The occurrence of nephrotoxicity within a few days of starting aminoglycoside in 4 patients suggests that antibiotics may not be the only cause in the development of nephrotoxicity. Likewise, Rossi et al²¹ reported that gentamicin had no adverse effects on renal functions in patients receiving ifosfamide therapy. However, nephrotoxicity in some patients may be attributed to the aminoglycoside usage during bacteremia. In our current series, only one patient developed nephrotoxicity in TBI-Cy conditioning regimen, and this limit the further statistical comparison between TBI-Cy and ICE arms in terms of other potential nephrotoxic agents.

The retrospective design of the analysis accounts for the main limitation of our study. Still, the randomized controlled trials remain the gold standard for the assessment of renal toxicity. In the absence of such trial, we found that TBI-Cy conditioning regimen seems not nephrotoxic than an ICE regimen particularly in patients who had used cisplatin prior to transplantation. Thus, TBI-Cy can be considered as an alternative-conditioning regimen for APSBCT in properly selected patients with high-risk of developing renal failure.

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