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Nephrotoxicity of cyclosporine A and amphotericin B-deoxycholate as continuous infusion in allogeneic stem cell transplantation

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Summary

Background: Nephrotoxicity is an important side effect of amphothericin B deoxycholate (ampho B) and cyclosporine A (CsA). The combined administration of these drugs is frequent in patients with haematological diseases undergoing allogeneic stem cell transplantation.

Aim: To assess the additional renal toxicity of ampho B given as a continuous infusion in addition to CsA.

Methods: In a retrospective study renal function was investigated in patients receiving CsA alone or in combination with ampho B (24-hour infusion) after allogeneic stem cell transplantation between January 1998 and April 2001.

Results: Of a total of 84 patients, 22 were treated with ampho B. There was a statistically significant decline in renal function in comparison to the 62 patients receiving CsA alone. However, renal insufficiency in all patients remained in a clinically acceptable range and was reversible. The residual renal dysfunction at the end of the hospitalisation was mainly due to continuing therapy with CsA.

Conclusion: Amphotericin B deoxycholate in addition to CsA leads to a statistically significant but clinically tolerable worsening of renal function. Using a 24-hour infusion and strict salt repletion, amphotericin B can be administered safely as deoxycholate in bone marrow transplant patients in conjunction with CsA for proven or suspected fungal infections.

Key words: amphotericin B; cyclosporine A; nephrotoxicitiy; allogeneic stem cell transplantation

Introduction

Patients with malignant haematological neoplasia, undergoing allogeneic stem cell transplantation receive several potentially nephrotoxic drugs in the conditioning and posttransplant phase. Among others these include cyclosporine A (CsA) for graft-versus-host disease (GVHD) prophylaxis and amphotericin B deoxycholate (ampho B) as empirical antifungal therapy in febrile neutropenic patients or in case of known invasive fungal infection [1]. The most common and serious side effect of ampho B is its often dose-limiting nephrotoxicity [2]. This is thought to be due to an acutely occurring vasoconstriction of the intrarenal arterioles with decreased renal blood flow and glomerular filtration rate, potentiated by hyponatraemia. It has been shown that infusions of saline improve renal function with a consecutive increased tolerance to ampho B [3]. A further mechanism is the membrano-toxic effect in renal tubular cells with enhanced membrane permeability that results in intracellular and tubular loss of potassium. The resulting renal tubular damage is diagnosed by hypokalaemia and metabolic acidosis. The high sensitivity of the tubular epithelium to ampho B may be explained by a restricted repair-mechanism in an acidotic environment [4]. The following factors increase the risk of renal insufficiency under ampho B: 1) total cumulated dose, 2) duration of therapy, 3) concomitant use of diuretics, 4) pre-existing renal dysfunction, 5) hypovolaemia and 6) additional use of other nephrotoxic substances (i.e. cyclosporine A, vancomycin) [4, 6]. Another important factor is the mode of ampho B administration. In a previous study, we have shown that continuous infusion of ampho B is better tolerated and at least as effective as application over 4 hours [7]. The same effect was observed in studies with liposomal formulation of ampho B, where a slower release of the drug is thought to be responsible for its better compatibility [8]. By using a 24-hour infusion, analogous to the liposomal formulation of ampho B, the glomerular component (vasoconstriction with decreased clearance and GFR) was improved. The

tubular dysfunction with tubular acidosis and loss of potassium did not differ [7]. In this study no patients on CsA were included. The following study therefore addresses nephrotoxicity of the simultaneous application of CsA as continuous infusion and ampho B in patients undergoing allogeneic stem cell transplantation.

Patients and methods

Subjects

During the period from January 1998 to April 2001, 86 patients underwent allogeneic stem cell transplantation at the University Hospital of Zurich. Two patients who had a syngeneic donor, without the need for immunosuppression, were excluded from the study. The 84 patients who underwent allogeneic (non-syngeneic) stem cell transplantation were observed in this retrospective trial to estimate the nephrotoxicity of amphotericin B (ampho B) in combination with cyclosporine A (CsA). Ampho B (Fungizone®, Bristol-Myers-Squibb) was administered as a continuous infusion in 500 ml of 5% dextrose without any additives through a separate intravenous line. In order to reduce nephrotoxicity all patients received an additional 1000 ml of normal saline over 24 hours as standard care whenever possible. Patients were divided into two groups depending on use of ampho B. 22 out of the 84 patients received ampho B in addition to CsA because of fever in neutropenia under broad-spectrum antibiotics or probable or proven invasive fungal infection (26% of all patients). Patients with probable invasive fungal infection had clinical evidence of pneumonia and characteristic findings on chest X rays or CT scans (nodules, wedge-shaped cavitating lesions, "halo-sign" or progression of lesions from infiltrates to cavitary or crescent lesions). Patients with possible invasive fungal infection were those with persistent fever and neutropenia who also had pulmonary infiltrates or sinus opacifications. The conditioning regimen consisted of total body irradiation (related donor 12 Gy, unrelated donor 13.2 Gy with lung shielding) in 51 patients, with busulfan and cyclophosphamide in 22 patients (26%) and various other regimens in 11 patients (13%). As graft-versus-host disease (GVHD) prophylaxis all patients received intravenous CsA (contin-

Table 1

Characteristics of all patients compared to treatment group with and without amphotericin B.

	all patients	without ampho B	with ampho B
characteristics*			
number of patients (%)	84 (100)	62 (74)	22 (26)
gender (female/male)	39/45	32/30	7/15
mean age ± SD (years)	35.2 ± 11.3	35.82 ± 12.01	33.63 ± 9.16
range (years)	17–59	17–59	18–54
weight ± SD (kg)	69.52 ± 16.91	69.35 ± 18.5	70 ±10.88
range (kg)	43–145	43–145	53–94
Diagnosis (%)			
AML	33 (39)	17 (27)[a]	16 (73)
CML	30 (36)	28 (45)[b]	2 (9)
ALL	11 (13)	9 (15)[c]	2 (9)
SAA	3 (4)	3 (5)	–
MDS	2 (2)	1 (1.6)	1 (4.5)
RAEB	2 (2)	1 (1.6)	1 (4.5)
OMF	1 (1)	1 (1.6)	–
NHL	1 (1)	1 (1.6)	–
WA	1 (1)	1 (1.6)	–
Conditioning regimes			
TBI (%)	51 (61)	32 (52)[d]	19 (86)
Bu-Cy (%)	22 (26)	22 (35)	0
others (%)	11 (13)	8 (13)	3 (14)
concomitant therapy (number of patients)			
Vancomycin %)	27 (32)	16 (26)	11 (50)
Fluconzale (%)	15 (18)	9 (15)	6 (27)
Itraconazole (%)	15 (18)	2 (3)	13 (59)
Teicoplanin (%)	12 (14)	5 (8)	7 (32)
Foscarnet (%)	4 (5)	1 (2)	3 (14)

* no statistical significant difference between group with and without amphotericin B (ampho B);
AML: acute myeloic leukemia; CML: chronic myeloic leukemia; ALL: acute lymphatic leukemia;
SAA: severe aplastic anemia; MDS: myelodysplastic syndrome; RAEB: refractory anemia with excess of blasts;
OMF: osteomyelofibrosis; NHL: non-Hodgkin lymphoma; WA: Wiskott-Aldrich syndrome;
TBI: total body irradiation; By-Cy: busulfan-cyclophosphamide.

[a] p-value = 0.003; [b] p-value = 0.045; [c] p-value <0.0001; [d] p-value = 0.0048

uous infusion over 24 hours) starting at day –1 with an initial dose of 10 mg/kg/day adjusted to whole blood levels of 500 to 750 ng/ml until day +7 and then adjusted to whole blood levels of 150–250 ng/ml. Methotrexate 15 mg/m^2 on day +1 and 10 mg/m^2 on day +3, +6, +11 together with intravenous immunoglobulines (0.5 g/kg/week) were administered as an additional GVHD prophylaxis.

Serum creatinine and potassium concentrations and through whole blood levels of CsA of all patients were determined at entry and at discharge respectively, at the begin and the end of ampho B therapy and peak values were compared with regard to the use of ampho B. The estimated creatinine clearance was calculated using the Cockroft-Gault formula (creatinine clearance = (150 – age) × weight/maximal creatinine concentration) [9].

Statistical analysis

Results are presented as means ± standard deviation (± SD). Nonparametric statistical tests were used throughout. Continuous variables between groups were compared using a two-tailed Mann-Whitney U test. Discontinuous variables were compared by the two-tailed Fisher's exact test. Statistical calculations were performed using InStat version 3.05 (GraphPad, San Diego, CA, USA). A p-value <0.05 was considered significant.

Results

The characteristics of the patients are given in table 1. In the 22 patients treated with ampho B the maximal dose ranged from 0.6 to 2 mg/kg/day with a duration of 3 to 112 days (table 2). No patient died from a fungal infection, neither during ampho B therapy nor during follow up at 3 and 6 months (table 2).

Table 3 compares parameters of kidney function in patients undergoing amphothericin B therapy (ampho B) with the patients receiving CsA alone. As surrogate measurements for glomerular filtration rate serum creatinine and the calculated clearance were investigated. The serum creatinine concentration did not differ between the two

Table 2

Characteristics of patients: treatment with amphotericin B.

Duration of administration (days)		22.3 ± 22.6	
Range (days)		3–112	
95% CI (days)		13.8–34.7	
Maximal dosage of ampho B (mg/kg body weight)		1.03 ± 0.37	
Range (mg/kg body weight)		0.6–2.0	
95% CI (mg/kg body weight)		0.8–1.1	
Total dose of ampho B (mg)		1181 ± 677	
Range (mg)		378–2655	
95% CI (mg)		844.5–1518.0	
Creatinine at end / creatinine at start of treatment		1.68 ± 0.59	
Range		0.76–3.09	
95% CI		1.42–1.94	
	start of ampho B therapy	**end of ampho B therapy**	**p-value**
CsA level (ng/ml)	259.2 ± 343.5	295.9 ± 241.2	0.173
Range (ng/ml)	0–1092	0–1214	
95% CI (ng/ml)	106.9–411.5	188.9–402.9	
Creatinine (µg/ml	83.7 ± 27.5	135.5 ± 52.8	<0.0001
Range (µg/ml)	52–177	59–282	
95% CI (µg/ml)	71.5–95.9	112.1–159.1	
Potassium (mmol/l)	3.5 ± 0.4	3.8 ± 0.7	0.192
Range (mmol/l)	2.8 –4.6	2.7–5.3	
95% CI (mmol/l)	3.3–3.7	3.4–4.1	
Outcome (cumulated)			
	end of ampho B therapy	**3 months posttransplant**	**6 months posttransplant**
Alive	19	18	14
Invasive fungal infection			
Proven or suspected (CT)	10	2	2
Pulmonary scars (CT)	3	8	6
No infiltrates	9	8	8
Antifungal therapy			
Stopped	4	5	4

Table 3

Results of all patients compared to treatment group with and without amphotericin B.

	all patients	without ampho B	with ampho B	p-value
Max. cyclosporine A concentration (ng/ml)	1118 ± 511	1240 ± 445	775 ± 539	0.0002
range (ng/ml)	0–2847	496–2847	0–2006	
95% CI (ng/ml)	107–1229	1127–1353	536–1015	
Creatinine at entry (µg/ml)	83.0 ± 16.3	81.9 ± 13.7	86.0 ± 13.7	0.5483
range (µg/ml)	58–173	58–134	69–173	
95% CI (µg/ml)	79.5–86.5	78.4–85.4	76.5–95.4	
Max. creatinine (µg/ml)	123.2 ± 41.3	111.0 ± 32.3	157.3 ± 45.3	<0.0001
range (µg/ml)	64–282	64–256	84–282	
95% CI (µg/ml)	114.2 ± 132.2	102.9–119.3	137.2–177.4	
Creatinine at discharge (µg/ml)	105.4 ± 42.6	96.1 ± 29.6	132.0 ± 59.6	0.0004
range (µg/ml)	57–291	57–258	68–291	
95% CI (µg/ml)	96.4–114.8	88.5–103.6	105.9–158.8	
Crea at discharge / Crea at entry (Tbv)	1.27 ± 0.42	1.17 ± 0.28	1.54 ± 0.60	0.0011
range	0.881–3.40	0.81–2.5	0.93–3.40	
95% CI	1.18–1.36	1.10–1.25	1.28–1.81	
Calculated min. creatinine clearance (ml/min)	69.3 ± 22.4	74.1 ± 21.7	55.5 ± 18.6	0.0002
range (ml/min)	32.7–149.0	32.9–149.0	32.7–99.6	
95% CI (ml/min)	64.4–74.1	68.6–79.6	47.3–63.8	
Minimal potassium concentration (mmol/l)	3.0 ± 0.3	3.1 ± 0.3	2.8 ± 0.4	<0.0001
range (mmol/l)	2.1–3.7	2.5–3.7	2.1–3.6	
95% CI (mmol/l)	2.9–3.0	3.0–3.1	2.5–2.9	
Creatinine 1 year after Tpl (µg/ml)	97.9 ± 25.0	91.9 ± 20.2	124.3 ± 29.3	<0.0001
range (µg/ml)	55–196	55–155	97–196	
95% CI (µg/ml)	91.3–104.5	86.0–97.0	104.5–143.9	
Blood pressure syst. 1 year after Tpl (mm Hg)	121.2 ± 14.6	120.9 ± 15.1	122.3 ± 12.9	0.8077
range (mm Hg)	90–160	90–160	105–145	
95% CI (mm Hg)	117.4–125.0	116.5–125.3	113.6–130.0	
Blood pressure diast. 1 year after Tpl (mm Hg)	77.5 ± 9.6	76.8 ± 9.7	80.5 ± 9.3	0.8711
range (mm Hg)	60–100	60–100	70–95	
95% CI (mm Hg)	75.0–80.0	74.0–79.7	74.2–86.7	

CsA: cyclosporine A; ampho B: amphothericin B; CI: confidence interval; Crea: Creatinine; Tbv: Times baseline value

groups at baseline: mean 81.9 ± 13.7 µg/ml in the group without ampho B and 86.0 ± 13.7 µg/ml in the group with ampho B (p = 0.548). During hospitalisation the renal function as assessed by serum creatinine and the calculated creatinine clearance decreased in all patients but with significantly greater decrease in the group receiving ampho B (table 3). In both groups none of the patients had a creatinine clearance below 30 ml/min. The minimal potassium concentration was significantly decreased in the group treated with ampho B, as a consequence of the tubular loss of potassium caused by ampho B. One year after transplantation a significant difference in serum creatinine level persisted (p <0.0001): group without ampho B 97.9 ± 25.3 µg/ml, group with ampho B 124.3 ± 29.3 µg/ml. Comparing systolic and diastolic blood pressure, there is no significant difference between the two groups (table 3).

Discussion

This retrospective study shows that amphothericin B deoxycholate (ampho B) can be safely administered as a continuous infusion in combination with cyclosporine A (CsA) in bone marrow transplant patients. While we found significantly higher ratios of peak serum creatinine to baseline creatinine concentrations in patients receiving ampho B, this loss of renal function was clinically tolerable in all instances. One year after transplantation there remains a significant difference between the two groups, but in no patient renal function is markedly restricted. A recent prospective randomised study compared the administration of ampho B either as a rapid (four

hours) or continuous infusion over 24 hours [7] mainly in patients with acute leukaemia without the use of CsA. Continuous infusion of ampho B showed a peak serum creatinine to baseline creatinine concentration of 1.25. In the present study this ratio was 1.45 in patients receiving ampho B in addition to CsA.. The results indicate that the combination of both agents increases the nephrotoxic effect as expected but in none of the patients did renal dysfunction necessitate premature termination of ampho B therapy. None of the creatinine-clearances calculated fell below 30 ml/min. Furthermore some of the patients included in our study were treated with other potentially nephrotoxic drugs (i.e. vancomycin, aminoglycosides). The high number of patients with acute myeloid leukaemia (AML) receiving ampho B can be explained by the more intensive pre-transplant treatment with repeated phases of aplasia and therefore a high incidence of pre-existing fungal infections. For the same reason many of the patients conditioned with total body irradiation (TBI) received ampho B, because mainly patients with AML were irradiated during their pre-transplant regimen. It has previously been shown that continuous infusion of ampho B deoxycholate reduces nephrotoxicity to the same extent to its incorporation into liposomes [7]. This study shows that amphotericin B deoxycholate can be safely administered together with high doses of CsA with no risk of detrimental renal dysfunction. It appears cautious to follow the practice of sodium chloride administration and to maintain serum potassium concentrations in the normal range. CsA blood levels should be monitored closely and dose adjustment made accordingly. As none of the 22 patients treated for suspected or proven fungal infection died from a mycosis the antifungal efficacy of continuous amphotericin B deoxycholate infusions also appeared to be satisfactory.

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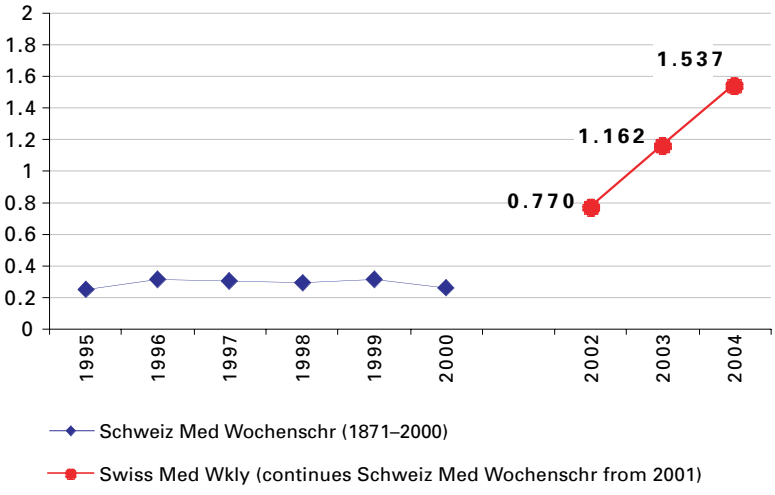

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