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W. Nürnberger · R. Willers · S. Burdach · U. Göbel

Risk factors for capillary leakage syndrome after bone marrow transplantation

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Abstract Age, hematopoietic growth factors, cyclosporin A, mode of bone marrow transplantation (BMT) (autologous, allogeneic-related, unrelated), and underlying disease were assessed as potential risk factors for capillary leakage syndrome (CLS) in 96 patients after BMT. CLS was defined as unexplained weight gain of >3% within 24 h and nonresponsiveness to furosemide. CLS occurred in 9/21 patients after unrelated compared with 2/33 after allogeneic-related BMT ($p=0.0017$) for hematopoietic disorders ($n=54$) and in 6/7 patients after allogeneic-related compared with 3/35 after autologous BMT ($p=0.0001$) for solid tumors ($n=42$). Hematopoietic growth factors and cyclosporin A were no signficant risk factors on their own. We conclude that unrelated BMTs or high-intensity conditioning regimens used in combination with allogeneic-related BMT are the main risk factors for CLS.

Key words Capillary leakage syndrome · Cytokines · Endothelial damage · Unrelated BMT · Pediatric solid tumors

Introduction

Capillary leakage syndrome (CLS) is characterized by loss of intravasal fluids into the interstitial space. Clinical findings include weight gain, generalized edema, hypotension, pre-renal failure, ascites, and pericardial and/or pleural effusions [18]. CLS has been described after infusion of interleukin-2 (IL-2) [18], tumor necrosis factor-α [17] and granulocyte-macrophage colony stimulating factor (GM-CSF) [10]. Following bone marrow transplantation (BMT), CLS was seen during acute graft-versus-host disease in the presence of high plasma levels of IL-2 [8]. Fatal outcomes of CLS after BMT have been described in patients who received total body irradiation (TBI) and high-dose cytarabine [22] or the combination of TBI, melphalan, and etoposide [14]. The definition of CLS is not standardized. Our definition of CLS is based on the increase of body weight over a short period of time [14]. This definition includes patients with an acute, severe onset of CLS and was the basis for this prospective investigation of potential risk factors for CLS.

W. Nürnberger (✉) · S. Burdach · U. Göbel
Department for Paediatric Haematology and Oncology, Heinrich Heine University Medical Center, Düsseldorf, Germany

R. Willers
University Computer Center, Heinrich Heine University, Düsseldorf, Germany

Methods and patients

Definition of CLS

CLS was defined as unexplained weight gain of more than 3% within 24 h (at least 0.5 kg), generalized edema, and nonresponsiveness to furosemide [14]. Fluid intake was restricted to 2 l/m^2 body surface area/day in nonfebrile patients. Perspiratio insensibilis was calculated as 600 ml/m^2 per day. Patients were weighed every 12 h and the central venous pressure was measured once daily via a Hickman catheter. Fluid intake and output were checked every 8 h. In case of fluid retention, furosemide was given in single doses of up to 3 mg/kg. If this was insufficient to achieve fluid balance, continuous infusions of furosemide were applied up to a cumulative total dose of 10 mg furosemide/kg body wt. per day.

Patients

From 1988 through 1996, 110 patients underwent BMT. The criteria of veno-occlusive disease for the liver include weight gain [12]. In order to have a clear case definition of CLS, patients with veno-occlusive disease ($n=14$) were excluded; the remaining 96 patients (median age: 11 years; range: 6 months to 31 years) were assessed. Supportive therapy was performed as described previously [5].

Forty-two patients (autologous BMT, $n=35$; allogeneic-related, $n=7$) had a solid tumor; of these, 17 patients received GM-CSF and 25 received G-CSF from day of transplantation until a stable engraftment was achieved.

Table 1 Patients' characteristics (*TBI* total body irradiation)

Diagnoses	(*n*)	Mode of transplantation	(*n*)	Conditioning regimens and references
Solid tumors	(42)			
– Ewing tumors	(28)	Autologous	(23)	TBI 12 Gy – etoposide 1800 mg/m^2 body surface area – melphalan 1800 mg/m^2 body surface area [4]
		Allogeneic-related	(5)	
– Rhabdomyosarcoma	(5)	Autologous	(4)	
		Allogeneic-related	(1)	
– Neuroblastoma	(8)	Autologous	(7)	
		Allogeneic-related	(1)	
– Lymphoepithelioma	(1)	Autologous	(1)	
Hematologic diseases	(54)			
–Acute lymphoblastic leukemia	(23)	Allogeneic-related	(13)	TBI 12 Gy – etoposide 60 mg/kg [2]
		Unrelated	(10)	TBI 12 Gy – etoposide 40 mg/kg – cyclophosphamide 120 mg/kg [20]
– Acute myelogenic leukemia	(17)	Allogeneic-related	(11)	Busulphan 16 mg/kg – cyclophosphamide 120 mg/kg [19]
		Unrelated	(6)	TBI 12 Gy – etoposide 40 mg/kg – cyclophosphamide 120 mg/kg [20]
– Chronic myelogenic leukemia	(7)	Allogeneic-related	(3)	Bulsulphan 16 mg/kg – cyclophosphamide 120 mg/kg [19]
		Unrelated	(4)	TBI 12 Gy – cyclophosphamide 120 mg/kg
– Severe aplastic anemia	(7)	Allogeneic-related	(6)	Total lymph node irradiation 5 Gy – cyclophosphamide 20–200 mg/kg [9]
		Unrelated	(1)	

Fifty-four patients had hematologic disorders (allogeneic-related BMT, $n=33$; unrelated BMT, $n=21$). Specified diagnoses and conditioning regimens are shown in Table 1.

GVHD prophylaxis

In the allogeneic-related constellation among children aged less than 10 years, prophylaxis for GVHD was performed as long-term treatment with methotrexate (MTX; 15 mg/m^2 body surface day +1, 10 mg/m^2 days +3, +6, +11 and then once weekly through day +100). Patients ≥10 years of age received cyclosporin A (CSA) plus short-term MTX (15 mg/m^2 day +1, 10 mg/m^2 days +3, +6, +11). CSA blood levels were measured three times a week and were adjusted to 300–400 ng/ml. Patients undergoing unrelated BMT received CSA, short-term MTX, and anti-IL-2 receptor (αp55) moAb (0.1 mg/kg per day from day ±0 to day +50, then tapered off until day +100 [4]).

Treatment prior to conditioning therapy

Patients with solid tumors ($n=42$), ALL ($n=23$), and AML ($n=17$) received high-dose chemotherapy prior to conditioning therapy. The cumulative pretreatment before BMT was assessed as "standard risk", i.e., for solid tumors: 12 courses of EVAIA chemotherapy [13] or Nbl-90 [1] polychemotherapy, and for ALL and AML: BMT in second complete remission (CR). Cumulative pretreatment was considered "high risk" in patients with solid tumors who had received more than 12 courses of EVAIA [13] and in patients with ALL or AML who received the BMT after second CR.

Risk factors and statistics

Age, haematopoietic growth factors (G-CSF vs GM-CSF), CSA, pretreatment before conditioning therapy (standard vs high risk), mode of BMT (autologous vs allogeneic-related vs unrelated), and underlying disease (solid tumor vs hematopoietic disorder) were assessed as potential risk factors for CLS. Mode of BMT and type of disease were assessed for inter-relationship since some of these were frequent combinations, e.g., "solid tumor" and "autologous BMT". The resulting combinations were analyzed using contingency tables (SAS program) as complete data set and in subgroups. A α-failure of <0.05 was considered to represent significancy, and a p–value of <0.01 was accepted, in order to correct for multiple calculations.

Results

Incidence of CLS

CLS occurred in 20/96 patients. Onset of CLS was between day +4 and day +17 (median: day +11) after BMT. The total body weight gain showed a median of 9.3% (range: 5.7–15.3%). All patients with CLS had pre-renal failure; five were dialyzed. Two patients developed lung edema requiring mechanical ventilation. Death from complications (until day +100 after BMT) occurred in 12/20 (60%) patients with CLS as compared with 11/76 (14%) patients without CLS ($p<0.0001$; df=1; $\chi^2=18.01$; Fisher's exact test).

Age and haematopoietic growth factors

CLS was not age dependent (data not shown). One of the 25 patients receiving G-CSF developed CLS compared with 3/17 patients receiving GM-CSF (not significant; Fisher's exact test).

Table 2 Incidence of CLS using the parameters "underlying disease" and "mode of BMT"

Combination of parameters[a]	CLS		Total
	Yes	No	
	no of patients/(%)		
Solid tumor, autologous	3 (9)	32 (91)	35 (100)
Solid tumor, allogeneic-related	6 (86)	1 (14)	7 (100)
Hematologic, allogeneic-related	2 (6)	31 (94)	33 (100)
Hematologic, unrelated	9 (43)	12 (57)	21 (100)
Total	20	76	96

Chi-square test: df = 3, $\chi^2 = 31.6$, $p < 0.001$
[a] The combinations "solid tumor, unrelated BMT" and "hematologic disease, autologous BMT" did not occur

GVHD prophylaxis

Of the 33 patients with hematologic disease and allogeneic-related BMT, 14 received only MTX and 19 received short-term MTX plus CSA. CLS occurred in 2/19 patients on MTX plus CSA and in none of the patients on MTX only (not significant, Fisher's exact test).

Mode of BMT and type of diagnosis

Although these parameters have six possible mathematical combinations, only four were observed in our patients (Table 2). The incidence of CLS was significantly higher in the group "allogeneic-related BMT, solid tumor" when compared with the corresponding patients with autograft (df = 1; $\chi^2 = 16.3$; $p = 0.0001$; Fisher's exact test), and when compared to patients with allogeneic-related transplants for hematological disorders (df = 1; $\chi^2 = 18.2$; $p < 0.0001$; Fisher's exact test). CLS was more frequent in the group "unrelated BMT, hematologic disease" than in the group "allogeneic-related BMT, hematologic disease" (df = 1; $\chi^2 = 8.6$; $p = 0.0017$; Fisher's exact test).

Pretreatment (prior to conditioning regimen)

This category was assessed for patients with solid tumors, ALL and AML (total number of patients: 82). Six of 53 patients had a standard pretreatment and developed CLS compared with 11 of 29 patients with high-risk pretreatment ($p = 0.0088$; Table 3).

Discussion

This prospective study confirms the high mortality among patients who develop CLS after BMT. Of all the parameters examined, either alone or in combination, the most important risk factor for CLS was the mode of BMT. Additional factors such as conditioning regimens with high toxicity may also play a role.

It has been suggested that CSA may cause endothelial damage/dysfunction [3] – a process which may induce capillary leakage. However, based on the 96 patients of this study, our results do not implicate CSA, G-CSF or GM-CSF, as independent primary risk factors for CLS after BMT.

The mode of BMT determines an allo-response. This depends on the disparity of the major and minor histocompatibility antigens between donor and recipient and is more pronounced in unrelated transplants. Moreover, disparity of the recipient/donor antigens may be amplified by intensive conditioning regimens [6]. This mechanism, together with an allogeneic-related mode of BMT, may contribute at least in part to the high rate of CLS in patients with solid tumors, all of whom received intensive radio/chemotherapy [5]. IL-2 has an important role in the allo-response and is involved in development of CLS [18]. This is in agreement with the observation, that severe CLS occurred following administration of IL-2 early after BMT [11].

Activation and damage of the endothelium during IL-2 infusion has been shown in skin biopsies [7]. Activated endothelial cells undergo structural changes which expose subendothelial structures to plasma proteins and may induce activation of the complement system [21]. Increased plasma levels of the complement activation product C5a, which is an inductor of edema, have been reported in CLS after BMT [15] and after IL-2 therapy [16].

Table 3 Incidense of CLS with respect to the cumulative pretreatment prior to BMT

Disorders	Pretreatment		Fisher's exact test
	Standard risk[a] *no. patients with CLS/ total no. of patients* (%)	High risk[a] *no. patients with CLS/ total no. of patients* (%)	
Solid tumors	3/23 (13)	6/19 (32)	
ALL/AML	3/30 (10)	5/10 (50)	
Total	6/53 (11)	11/29 (38)	$p = 0.0088$

[a] For definition of standard risk and high risk see "Material and methods" section

In conclusion, the parameters (a) unrelated BMT and (b) allogeneic-related BMT in combination with intensive conditioning regimens or increased cumulative chemotherapy prior to the conditioning regimen were identified as risk factors for CLS. These basic parameters must be considered in evaluation of therapeutic interventions for CLS, e.g., inhibition of activated complement system by C1 esterase inhibitor concentrate [15].

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