Incidence and Outcome of Hepatic Veno-Occlusive Disease After Blood or Marrow Transplantation: A Prospective Cohort Study of the European Group for Blood and Marrow Transplantation

By Enric Carreras, Hartmut Bertz, William Arcese, Jean-Paul Vernant, José-Francisco Tomás, Hans Hagglund, Giuseppe Bandini, Hèléne Esperou, James Russell, Javier de la Rubia, Gabriele Di Girolamo, Hilde Demuynck, Olivier Hartmann, Johannes Clausen, Tapani Ruutu, Veronique Leblond, Arturo Iriondo, Alberto Bosi, Isaac Ben-Bassat, Vladimir Koza, Alois Gratwohl, and Jane F. Apperley on behalf of the European Group for Blood and Marrow Transplantation Chronic Leukemia Working Party

To determine the incidence and outcome of hepatic veno-occlusive disease (VOD) after blood or marrow transplantation (BMT), we prospectively evaluated all consecutive patients receiving a BMT during a 6-month period in participating EBMT centers. All of them were evaluated for occurrence of VOD according to previously defined clinical criteria. The clinical course, outcome, value of prophylactic and therapeutic interventions, and the influence of previously described risk factors were analyzed. During the study period, 1,652 BMT were performed in 73 centers. VOD was diagnosed in 87 patients (5.3%; 95% confidence interval [CI], 4.2% to 6.4%). Fifty-six of 631 allogeneic BMT (8.9%) and 31 of 1,010 autologous BMT (3.1%) developed this complication ($P < .0001$). VOD was classified as mild in 7 (8%), moderate in 56 (64.4%), and severe in 24 (27.6%) cases. Sixteen patients died of VOD (corresponding to 1% of the whole series, 18.4% of VOD patients, and 66.7% of severe VOD). The use of unfractionated heparin did not significantly decrease the incidence of VOD. Independent variables associated with an increased risk of VOD were allogeneic BMT (relative risk [RR], 2.8; $P < .001$), pre-BMT elevation of serum aspartate aminotransferase (RR, 2.4; $P = .001$), high-dose cytoreductive therapy (RR, 2.3; $P = .003$), Karnofsky performance score less than 90% (RR, 2.7; $P = .006$), and prior abdominal radiation (RR, 2.9; $P = .03$). In conclusion, this prospective study shows that (1) the incidence of VOD is lower than that reported in smaller studies from single centers, (2) about one fourth of cases of VOD progress to severe disease, (3) main risk factors have a major impact on incidence of VOD, and (4) the use of prophylactic unfractionated heparin does not seem to reduce the incidence of VOD.

LIVER DAMAGE IS A common complication of cytoreductive therapy used for blood or bone marrow transplantation (BMT).[1,2] The most prominent site of damage is zone 3 of the liver acinus. Hepatic venular occlusion, hepatic venular eccentric luminal narrowing, phlebosclerosis, sinusoidal fibrosis, and hepatocyte necrosis are the most common histologic features of this damage.[3] The clinical syndrome resulting from this hepatic toxicity is commonly called veno-occlusive disease of the liver (VOD), and it is characterized by hyperbilirubinemia, fluid retention, and painful hepatomegaly appearing soon after BMT.[1,2,4] Because the high bleeding risk in the early transplant phase precludes a percutaneous liver biopsy, clinical criteria for the diagnosis of VOD have been developed by both the Seattle[4,5] and Baltimore groups.[6] VOD has been considered a frequent and often fatal complication of BMT. Results of large series of patients reported incidences up to 53% and a case fatality rate up to 47%.[4-6] Nevertheless, review of the literature shows that the incidence of VOD ranges from 0% to 70% and that its fatality rate can be as low as 3%.[1,2,7] The reason for this disparity is unknown. It most likely reflects diverse criteria for diagnosis, small sample size, and variable distribution of risk factors for VOD in the different series. To better determine the incidence, clinical course, and outcome of VOD after BMT, the EBMT Chronic Leukemia Working Party performed a prospective survey among EBMT teams.

PATIENTS AND METHODS

Patients

Study design. Prospective evaluation of all consecutive patients receiving a BMT in participating centers between November 1, 1995 and April 30, 1996.

Patient population. During this 6-month period, 6,795 BMT (4,697 autologous and 2,098 allogeneic) were performed in 367 EBMT centers. Seventy-five of these centers participated in this prospective study. Two of them reported cases of VOD but did not report simultaneous patients who had not developed VOD. These cases were therefore not included in the final analyses. The remaining 73 centers (see Appendix) reported 1,652 patients. This cohort represents 24% of all EBMT transplants during this period. The proportion of allogeneic and syngeneic BMT in the cohort was slightly higher than in the whole group (38% *v* 31% and 0.6% *v* 0.3%, respectively; $P < .001$; Table 1). The median number of transplants per center was 21 (range, 2 to 87).

From Hospital Clinic, IDIBAPS, Barcelona, Spain; University of Freiburg, Freiburg, Germany; Universita degli Studi La Sapienza, Rome, Italy; Hôpital Henri Mondor, Creteil, France; Hospital de la Princesa, Madrid, Spain; Huddinge Hospital, Huddinge, Sweden; Hospital San Orsola, Bologna, Italy; Hôpital Saint Louis, Paris, France; Foothills Hospital, Calgary, Alberta, Canada; Hospital La Fe, Valencia, Spain; Ospedale Civile, Pescara, Italy; University Hospital, Leuven, Belgium; Institut Gustave Roussy, Villejuif, France; Universitätskrankenhaus Eppendorf, Hamburg, Germany; Helsinki University Central Hospital, Helsinki, Finland; Hôpital Pitié Salpétrière, Paris, France; Hospital Marqués de Valdecilla, Santander, Spain; Ospedale di Careggi, Firenze, Italy; Sheba Medical Center, Tel-Hashomer, Israel; Charles University Hospital, Pilsen, Czech Republic; Kantonsspital, Basel, Switzerland; and Hammersmith Hospital, London, UK.

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Address reprint requests to Enric Carreras, MD, BMT Unit, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain; e-mail: bmtunit@medicina.ub.es.

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Table 1. EBMT Survey on VOD: Cohort Characteristics

	EBMT	Study Cohort
Participant centers	367	73 (20%)
BMT performed during study period*	6,795	1,652 (24%)
Allogeneic	2,079 (31%)	631 (38%) $P < .001$
Syngeneic	19 (0.3%)	11 (0.6%)
Autologous	4,697 (69%)	1,010 (61%)

*November 1, 1995 to April 30, 1996.

Data Collection

By means of a very simple questionnaire, we collected information on type of transplant (allogeneic or autologous), type of donor (HLA identical sibling, other relative, unrelated donor, or twin), risk factors for VOD (see below), prophylactic measures (none, unfractionated heparin, low molecular weight heparin, prostaglandin E1, ursodeoxycholic acid, and others), sodium heparin for flushing central venous lines (yes/no; daily dose), diagnosis of VOD (2 or 3 clinical criteria [see definitions], histologic confirmation [yes/no], hemodynamic study [yes/no; hepatic venous pressure gradient][8,9]), treatment of VOD (none, fluids and sodium restriction, heparin, recombinant tissue plasminogen activator, antithrombin III, prostaglandin E1, and others), resolution of VOD (yes/no), and death due to VOD (yes/no).

Definitions

VOD. The diagnosis of VOD was established in each participating center according to previously described clinical criteria, ie, occurrence of two or more of the following events before day 21 after hemopoietic progenitor cell administration: hyperbilirubinemia (>34.2 μmol/L or >2 mg/dL), ascites or sudden weight gain (>5% of baseline body weight), and painful hepatomegaly. No other explanation for these signs and symptoms (septicemia, cyclosporin toxicity, heart failure, hepatitis, etc) could be present at the time of diagnosis.

Risk factors for VOD. Two categories of factors previously associated to the development of VOD[1,3,6,7,10] were analyzed: (1) patient-related factors, ie, age greater than 20 years, previous radiation therapy of the abdomen, second BMT, previous liver disease, increased serum aspartate aminotransferase (AST) before cytoreductive therapy, Karnofsky performance score less than 90%, and presence of fungal infection 1 week before BMT; and (2) transplant-related factors, ie, type of transplant, type of donor, pretransplant acyclovir therapy, vancomycin administration during cytoreductive therapy, and dose of cytoreductive therapy. As previously reported,[4] regimens considered as high-dose cytoreductive therapy were those either including both busulfan and cyclophosphamide (Cy), or Cy and total body irradiation with a total radiation dose greater than 12 Gy, or Cy and BCNU and etoposide, or those with an equivalent intensity. The remaining regimens were classified as low-dose cytoreductive therapy.

Clinical course and outcome of VOD. In cases of VOD, measures used for the treatment of VOD and the evolution of VOD were evaluated. Those with a self-limiting VOD, ie, not requiring treatment, were classified as having mild VOD. Those with a complete resolution of all signs of liver damage but requiring treatment (sodium restriction, diuretics, analgesics, etc) were classified as having moderate VOD. Those whose liver damage did not resolve before day 100 or the patient died, whichever occurred first, were classified as having a severe VOD.[4] To evaluate these patients, additional information by day 100 posttransplant was required from all centers reporting cases that had not resolved by the end of the study.

Statistical Methods

Associations between VOD and prophylactic measures and patient- and transplant-related variables were tested in univariate analyses using χ^2 statistics or Fisher's exact test as appropriate. Significant variables at the $P < .1$ level were fitted to a multiple logistic regression model using forward stepwise variable selection. The relative risk of VOD associated with a single risk factor was computed as the probability of VOD for patients with that risk factor divided by the probability of disease for patients without that risk factor (BMDP Statistical Software, Los Angeles, CA). Additionally, the relative risk of VOD of patients with a risk factor was computed as the probability of VOD for patients with this risk factor divided by the probability of disease for patients with none of the examined risk factors.[11] Finally, the cumulative probability and relative risk of VOD of patients with more than one risk factor was calculated.

RESULTS

Incidence of VOD

VOD was diagnosed in 87 of 1,652 patients (5.3%; 95% confidence interval [CI], 4.2% to 6.4%). Fifty-four (62%) fulfilled two clinical criteria for VOD, whereas the remaining 33 (38%) had three clinical criteria. In 15 cases (17.2%), VOD was confirmed by means of a liver biopsy; only 4 (4.6%) were evaluated by a hemodynamic study. VOD was observed in 56 of 631 allogeneic BMT (8.9%) and in 31 of 1,010 autologous BMT (3.1%; $P < .0001$). There were no cases of VOD among patients receiving syngeneic BMT (Table 2).

Influence of Risk Factors for VOD

Table 3 shows the incidence of VOD according to evaluated risk factors. In univariate analysis, the incidence of VOD was higher in allogeneic BMT than in autologous BMT (8.9% *v* 3.1%; $P < .0001$). The donor type did not influence VOD incidence, ie, HLA-identical sibling (9.8%), versus other relative (5%), versus unrelated donor (6.8%). The incidence of VOD was higher among patients with increased serum AST level before cytoreductive therapy (13.3% *v* 4.6%; $P < .0001$), with previous liver disease (12.8% *v* 4.9%; $P = .0013$), with high-dose conditioning (6.6% *v* 2.4%; $P = .0003$), with previous radiation therapy to the abdomen (13.2% *v* 5%; $P = .009$), and with Karnofsky performance score less than 90% before transplant (13% *v* 4.7%; $P = .0002$). The remaining risk factors analyzed did not influence the incidence of VOD. Independent variables associated with an increased risk of VOD in logistic regression analysis were (Table 3) allogeneic BMT

Table 2. Incidence and Outcome of VOD

Incidence of VOD	No. With VOD/No. Evaluated
Whole series	87/1,652 (5.3%)
Autologous BMT	31/1,010 (3.1%)
Syngeneic BMT	0/11
Allogeneic BMT	56/631 (8.9%)
HLA-identical sibling	45/458 (9.8%)
Other relative	2/40 (5.0%)
Unrelated donor	9/133 (6.8%)
Outcome	**No./Total**
Mild VOD	7/87 (8.0%)
Moderate VOD	56/87 (64.4%)
Severe VOD	24/87 (27.6%)
Death due to VOD	16/87 (18.4%)*
Not resolved†	8/87 (9.2%)

*One percent of the whole series; 66.7% of severe VOD.
†When the patient died of other causes.

Table 3. Univariate and Multivariate Analyses of Risk Factors for Hepatic VOD

Factor	No. With VOD/ No. Evaluable (%)	Univariate Analysis *P* Value	Multivariate Analysis *P* Value	RR (95% CI)
Patient-related factors				
Age >20 yr				
No	21/306 (6.9)	NS		
Yes	66/1,346 (4.9)			
Previous abdominal radiation				
No	80/1,599 (5.0)	.009	.03	2.9
Yes	7/53 (13.2)			(1.2-6.9)
Second BMT				
No	84/1,617 (5.2)	NS		
Yes	3/35 (8.6)			
Previous liver disease				
No	76/1,566 (4.9)	.0013		
Yes	11/86 (12.8)			
Increased serum AST level				
No	70/1,524 (4.6)	<.0001	.001	2.4
Yes	17/128 (13.3)			(1.3-4.3)
Karnofsky score <90%				
No	73/1,544 (4.7)	.0002	.006	2.7
Yes	14/198 (13.0)			(1.4-5)
Fungal infection before BMT				
No	86/1,637 (5.3)	NS		
Yes	1/15 (6.7)			
Transplant-related factors				
Pretransplant acyclovir				
No	71/1,381 (5.1)	NS		
Yes	16/271 (5.9)			
Vancomycin during CT				
No	77/1,514 (5.1)	NS		
Yes	10/138 (7.2)			
Dose of CT				
Low	13/539 (2.4)	.0003	.003	2.3
High	74/1,113 (6.6)			(1.2-4.2)
Type of transplant				
Allogeneic	56/631 (8.9)	<.0001	<.001	2.8
Autologous	31/1,010 (3.1)			(1.8-4.4)

Abbreviations: CT, cytoreductive therapy; AST, aspartate aminotransferase; NS, not significant.

(relative risk [RR], 2.8; $P < .001$), pre-BMT increased serum AST (RR, 2.4; $P = .001$), cytoreductive therapy with a high-dose regimen (RR, 2.3; $P = .003$), Karnofsky performance score less than 90% (RR, 2.7; $P = .006$), and previous abdominal radiation (RR, 2.9; $P = .03$). Similar results were obtained when the end-point of univariate and multivariate analyses were severe VOD or to die of VOD. Thus, the variables associated with a higher risk of this last complication were allogeneic BMT (RR, 2.8; $P < .001$), high-dose cytoreductive therapy (RR, 2.3; $P = .004$), pre-BMT increased serum AST (RR, 2.1; $P = .01$), previous abdominal radiation (RR, 2.9; $P = .05$), and Karnofsky performance score less than 90% (RR, 2.7; $P = .06$).

Depending on the presence or absence of these risk factors, the relative risk of VOD ranged from 1 to 13.6 (Table 4). Table 5 shows the influence of these risk factors on the incidence of VOD in the patients included in this survey. Those patients without risk factors for VOD receiving an autologous BMT had an incidence of VOD lower than 1%, whereas those with three risk factors had incidences ranging from 25% to 29%.

Table 4. RR of VOD Depending on Main Risk Factors

	KI >90 and Normal AST	>AST	KI <90	>AST + KI <90
Auto BMT				
Low-dose CT	1 (3.9)	3.7 (6.6)	3.2 (6.2)	6.4 (8.9)
High-dose CT	3.3 (6.2)	5.9 (8.9)	5.5 (8.4)	8.2 (11)
AlloBMT				
Low-dose CT	3.7 (6.6)	6.4 (9.3)	5.9 (8.9)	8.6 (11.5)
High-dose CT	5.9 (8.7)	8.6 (11.5)	8.2 (11)	10.8 (13.6)

RR of VOD respecting patients with none of the main risk factors. Values in brackets are the RR of patients with previous abdominal radiation as an additional risk factor.

Abbreviations: CT, cytoreductive therapy; KI, Karnofsky performance score; AST, aspartate aminotransferase.

Influence of VOD Prophylaxis

The small number of patients receiving low molecular weight heparin (n = 66), prostaglandin E1 (n = 22), or ursodeoxycholic acid (n = 31) precluded an adequate evaluation of their prophylactic effect. The use of prophylactic unfractionated heparin was not associated with a lower incidence of VOD. Because most patients receiving prophylactic heparin were patients who were at high risk of developing VOD, the efficacy of unfractionated heparin among patients with none, one, two, or three risk factors for VOD was analyzed. Heparin did not significantly reduce the incidence of VOD in any of these subgroups. Similarly, the use of heparin to flush central venous lines as well as the total daily dose of heparin used for this purpose were not associated with a different incidence of VOD (Table 6).

Outcome of Patients With VOD

Seven cases of VOD (8%) were classified as mild, 56 (64.4%) as moderate, and 24 (27.6%) as severe. All patients classified as having moderate/severe VOD had fluid and sodium restriction associated with one or more of the following measures: diuretics (n = 66), heparin (n = 17), recombinant tissue plasminogen activator (n = 12), antithrombin III (n = 3), prostaglandin E1 (n = 10), and other unspecified treatments

Table 5. Influence of Main Risk Factors on the Incidence of VOD in the Patients Included in This Survey

	KI >90 and Normal AST	>AST	KI <90	>AST + KI <90
AutoBMT				
Low-dose CT	0.9%	14.3%	0%	NC
High-dose CT	3.3%	6.8%	11.1%	28.6%
AlloBMT				
Low-dose CT	3.9%	25%	NC	NC
High-dose CT	7.5%	11.4%	25%	NC

Abbreviations: CT, cytoreductive therapy; KI, Karnofsky performance score; AST, aspartate aminotransferase; NC, no cases presented these risk factors.

Table 6. Influence of Prophylactic Measures on Incidence of VOD

Prophylaxis	No. With VOD/No. Evaluable (%)	*P* Value
LMWH		
No*	31/660 (4.7)	
Yes	4/66 (6.1)	NS
UDCA		
No*	31/660 (4.7)	
Yes	0/31	NS
PGE1		
No*	31/660 (4.7)	
Yes	2/22 (9.1)	NS
Unfractionated heparin		
No*	31/660 (4.7)	
Yes	25/335 (7.5)	NS
Patients without risk factors		
Heparin		
No*	1/180 (0.5)	
Yes	1/65 (1.5)	NS
Patients with one risk factor		
Heparin		
No*	6/258 (2.3)	
Yes	10/137 (7.3)	.01
Patients with two risk factors		
Heparin		
No*	13/173 (7.5)	
Yes	11/115 (9.6)	NS
Patients with three or more risk factors		
Heparin		
No*	11/43 (25.6)	
Yes	3/18 (16.7)	NS
Heparin for flushing central lines		
No*	30/660 (4.5)	
Yes	26/540 (4.8)	NS
Dose of heparin used for catheter maintenance		
<1,000 U/d	13/221 (5.9)	
1,000-5,000 U/d	11/215 (5.1)	
>5,000 U/d	2/80 (2.5)	NS

Abbreviations: LMWH, low molecular weight heparin; UDCA, ursodeoxycholic acid; PGE1, prostaglandin E1; NS, not significant.

*Patients with neither systemic prophylaxis nor heparin for flushing central venous lines.

(n = 7). There were not enough cases of VOD in our series to evaluate the impact of these therapeutic measures on evolution.

Sixteen patients with a severe disease died of VOD during the first 100 days posttransplant. This represents 1% of the whole series, 18.4% of cases of VOD, and 66.7% of cases with severe VOD. The mortality rate was similar among autologous and allogeneic BMT (22% *v* 16%) and significantly lower among patients with two clinical features of VOD than in those with three features (5.6% *v* 30.3%; $P = .005$). Liver damage was not resolved in 8 (9%) patients when they died of other causes (Table 2).

DISCUSSION

Eighty-seven of 1,652 (5.3%) transplant recipients (8.9% of allogeneic and 3.1% of autologous) developed VOD in this prospective survey. This is in accordance with the incidence reported in preliminary series,[12-18] another multicentric analysis,[10] a previous EBMT interim analysis (incidence of VOD 4%; unpublished), and the largest series from a single center.[19] However, it contrasts with three large series on VOD in allogeneic and autologous BMT recipients.[4-6] The first series was reported in 1984 by the Seattle group. In this retrospective analysis, using the current worldwide accepted clinical criteria for diagnosis of VOD for the first time, the incidence of VOD was 22% and the mortality rate 47%.[5] In 1987, the Baltimore group, using their own clinical criteria for the diagnosis of VOD, reported an incidence of 21% with a fatality rate of 45%.[6] Finally, in 1993, the Seattle group prospectively evaluated 355 consecutive patients receiving a BMT between 1987 and 1988 and modified their initial clinical criteria slightly. The incidence of VOD was 54% and the liver dysfunction caused or contributed to death in 28% of cases.[4]

The different incidence of VOD between series may be related to the variable incidence of risk factors, patient selection, and the definition of VOD. Thus, most patients included in the Seattle prospective analysis received an allogeneic BMT with high-dose cytoreductive therapy.[4] In contrast, only 29% of patients transplanted in Europe during this 6-month period received high-dose regimens and allogeneic BMT; furthermore, 21% of them did not have any risk factor for VOD. When patients with several risk factors for this complication were analyzed, the incidence of VOD was similar to the one described in the Seattle and Baltimore reports.

Multivariate analysis confirmed the impact of most of the previously described risk factors for VOD such as serum AST level before BMT, dose of cytoreductive regimen, Karnofsky performance score, and prior abdominal radiation. Despite the clinical impression by numerous physicians that VOD was less common after autologous BMT when compared with allogeneic BMT, three large multivariate analyses failed to confirm this impression.[4-6] However, two previous reports from the Seattle group suggested that comparably treated patients undergoing autologous BMT developed VOD less frequently than allogeneic BMT.[20,21] Our analysis corroborates this observation, because the type of transplant was one of the most important risk factors for VOD in our series (RR, 2.8). This observation could not be attributed to a higher incidence of high-dose conditioning regimens among patients receiving an allogeneic BMT. Thus, when comparing allogeneic and autologous BMT receiving high-dose cytoreductive therapies, allogeneic BMT also had a higher incidence of VOD (9.7% *v* 4.3%; $P = .0004$). Nevertheless, the higher incidence of VOD described by other investigators[4] among allogeneic BMT from unrelated donors was not observed. This could be attributed to the fact that most unrelated BMT performed in Europe during 1995/1996 were donor-recipient pairs typed by high-resolution methods, whereas patients included in the Seattle study were evaluated by means of less sensitive typing methods.

The small number of patients receiving low molecular weight heparin, prostaglandin E1, and ursodeoxycholic acid and the low incidence of VOD precluded an adequate evaluation of their efficacy in the prevention of this complication. We could not confirm the previously reported preventive effect of unfractionated heparin administration.[22] This absence of efficacy, also reported by other investigators,[19,23,24] persisted even when analyzing subgroups of high-risk patients. This observation

stresses the need for carefully conducted studies on VOD prophylaxis in selected high-risk patient population.

The evolution of VOD in our survey was similar to that described in other series. Thus, one fourth of cases of VOD had severe VOD and almost 70% of them died of VOD. The diversity of treatments used and the small number of patients with VOD precluded any analysis of therapeutic measures.

In conclusion, this prospective survey shows that (1) the incidence of VOD is lower than previously reported in smaller studies from single centers; (2) about one fourth of cases of VOD progress to severe disease; (3) risk factors such as allogeneic BMT, elevated transaminase values before transplantation, high-dose cytoreductive therapy, low performance score, and previous abdominal radiation have a major impact on incidence of VOD; and (4) the use of prophylactic unfractionated heparin does not seem to reduce the incidence of VOD.

APPENDIX

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