

## LETTER TO THE EDITOR

# Incidence and management of hepatic venoocclusive disease in 237 patients undergoing reduced-intensity conditioning (RIC) haematopoietic stem cell transplantation (HSCT)

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Hepatic venoocclusive disease (VOD) is a clinical syndrome comprising of hyperbilirubinaemia, painful enlargement of the liver, ascites and weight gain with a typical onset by day 30 following haematopoietic stem cell transplantation (HSCT). Diagnosis is confirmed by liver histology and differential diagnoses such as hepatic graft-versus-host disease (GVHD), drug-induced cholestasis and sepsis have to be excluded. The dose intensity of conditioning regimens has an important effect on the subsequent development of VOD. A 6-month prospective European Group for Blood and Marrow Transplantation study reported an incidence of VOD post autologous and allogeneic bone marrow transplantation at 3.1 and 8.9%, respectively.<sup>1</sup> Indeed, following myeloablative conditioning with high-dose cyto-reductive therapy ± total body irradiation (TBI), the incidence of VOD has been reported to be as high as 54%.<sup>2</sup> In contrast, using a non-myeloablative conditioning regimen with 2 Gy TBI ± fludarabine, the MD Anderson group reported hyperbilirubinaemia in 84% of patients receiving allogeneic transplants, but with no reports of VOD.<sup>3</sup> VOD is a significant cause of morbidity and mortality following allogeneic HSCT, with limited treatment options. Anticoagulants and antifibrinolytic agents such as heparin, and tissue plasminogen activator, which prevent microvascular thrombosis and may reduce hepatic sinusoidal injury, have been used with limited success. Defibrotide (DF) is the sodium salt of a single-stranded polydeoxyribonucleotide with anti-ischaemic, anti-inflammatory and thrombolytic without significant anticoagulant property. Recently, DF has shown promise in prophylaxis and treatment of VOD following allogeneic transplantation. We have retrospectively reviewed the incidence of VOD among patients treated with reduced-intensity conditioning (RIC) HSCT at our centre, and evaluated the use of DF to treat patients with VOD (Table 1).

Two hundred and thirty-seven non-myeloablative allografts were performed from January 1999 to December 2004. The median recipient age was 51 years (range: 19–72 years). Patients were conditioned with BCNU/etoposide/cytarabine/alemtuzumab ( $n=37$ ), fludarabine/melphalan/alemtuzumab ( $n=26$ ) for lymphoid disorders (non-Hodgkin's lymphoma, Hodgkin's disease, chronic lymphocytic leukaemia, myeloma) and fludarabine/busulphan/alemtuzumab (chronic myelogenous leukaemia, myelodysplastic syndrome, acute myelogenous leukaemia) ( $n=174$ ) for

myeloid disorders. Forty-five patients had a previous HSCT (21 autografts, 24 allografts). During pre-transplantation assessment, 10 patients were noted to have impaired baseline liver function tests (LFTs) and an additional eight patients had serological evidence of past hepatitis B infection. All patients had LFTs and body weight monitored daily until discharge and twice weekly thereafter for the first 3 months. Cyclosporine levels were performed daily as inpatient and twice weekly as outpatient. All suspected patients had liver imaging and comorbid events such as sepsis, GVHD and hepatotoxic drug exposure were excluded wherever possible. Clinical diagnosis of VOD was determined based on previously described criteria.<sup>4</sup>

Fourteen out of 237 (5.9%) patients were diagnosed with VOD. Six patients had received stem cells from a human leucocyte antigen (HLA)-matched unrelated donor and eight patients from an HLA-matched sibling donor. The median age of the patients was 48 years (range: 26–57 years) and the median time to the onset of VOD following transplantation was 10.5 days (range: 4–183 days). Twelve patients had oral busulphan as part of conditioning and one patient received mylotarg 32 days post transplant. Six patients had a previous HSCT (five allograft and one autograft). At the time of diagnosis, two patients had grade II and grade III cutaneous GVHD, respectively. Liver biopsy was not performed in any patients owing to the high risk of bleeding. All patients were commenced on DF (Gentium SpA) within 48 h of diagnosis. Ten out of 14 (71%) patients received a dose of 40 mg/kg/day whereas 4/14 received doses between 10 and 20 mg/kg/day. Median duration of therapy was 13 days (range: 3–22 days). Complete resolution of VOD was observed in 3/14 (22%) with partial and no response noted in 5/14 (35%) and 6/14 (44%), respectively. DF was discontinued in two patients owing to gastrointestinal haemorrhage. Multi-organ failure occurred in five patients, and was fatal in four (80%) patients. Mortality at day 100 was 6/14 (44%), with a 1-year mortality of 10/14 (71%). On univariate analysis, prior allogeneic HSCT was the only variable associated with an increased risk of developing VOD ( $P=0.005$ ).

We report on a retrospective study of 237 patients undergoing RIC HSCT, with a low incidence of hepatic VOD (5.7%). In comparison, the incidence of VOD in patients who underwent myeloablative HSCT during the same period at our centre was 11.9% ( $n=59$ ). The majority of patients who developed VOD received significant amounts of chemotherapy before transplantation. Six patients had a previous HSCT (five allografts, one autograft). Of the remaining eight patients, three patients

**Table 1** Patient characteristics and treatment details

Age/sex	Diagnosis	Previous treatment	Conditioning regimen	Onset of VOD	Duration of DF therapy	Dose of DF therapy (mg/kg)
54/F	Follicular NHL	COP/chlorambucil	Beam/alemtuzumab	9	5	40
53/F	AML M6	Sibling allograft	Flag-Ida/alemtuzumab	9 <sup>a</sup>	8	40
44/F	Hodgkin's disease	Previous autograft	Flu/Mel/alemtuzumab	8	7	15
57/M	Myelofibrosis	Previous RIC VUD	Flu/Bu/alemtuzumab	5	17	40
45/F	MDS RCMD	Flag-Ida	Flu/Bu/alemtuzumab	183 <sup>b</sup>	4	40
45/M	CML	RIC allograft/Flag-Ida	Flu/Bu/alemtuzumab	106 <sup>a</sup>	13	40
26/F	Pre B-ALL	TBI/etoposide allograft/Flag	Flu/Mel/alemtuzumab	11	6	10
55/M	CLL	FMD, alemtuzumab	Beam/alemtuzumab	12	16	40
38/M	CMML	Flag	Flu/Bu/alemtuzumab	10	19	40
56/M	Myelofibrosis	Flag	Flu/Bu/alemtuzumab	11	13	40
48/F	T-PLL	Pentostatin, alemtuzumab	Beam/alemtuzumab	8	15	20
48/M	MDS RARS	Thalidomide	Flu/Bu/alemtuzumab	16	12	40
38/M	Low grade NHL	Chlorambucil/CVP-R	Beam/alemtuzumab	11	22	40
57/M	Follicular NHL	Flu/Mel/alemtuzumab	Flu/Bu/alemtuzumab	12	4	10

Abbreviations: ALL = acute lymphoblastic leukaemia; AML = acute myelogenous leukaemia; CLL = chronic lymphocytic leukaemia; CMML = chronic myelomonocytic leukaemia; DF = defibrotide; F = female; M = male; MDS = myelodysplastic syndrome; NHL = non-Hodgkin's lymphoma; RARS = refractory anaemia with ringed sideroblast; RIC = reduced-intensity conditioning; TBI = total body irradiation; VOD = venoocclusive disease.

<sup>a</sup>Coexistent graft-versus-host disease.

<sup>b</sup>Mylotarg therapy 32 days before VOD.

had at least two lines of therapy for their primary disease and one patient had received mylotarg post HSCT for disease relapse.

DF has been used for treatment and prophylaxis of hepatic VOD. Richardson *et al.*<sup>5</sup> used DF on a compassionate basis in 88 patients with hepatic VOD. Despite 97% of patients having multiorgan failure, complete remission of VOD was observed in 36%, with an overall survival at day 100 of 35%. Most responses were seen at doses 20 mg–40 mg/kg/day with significant reduction of plasminogen activator inhibitor levels 1. In our study, a similar clinical response was seen with complete and partial responses in 8/14 patients with only two patients experiencing significant side effects of therapy.

In conclusion, VOD occurs at a lower incidence in patients undergoing RIC HSCT. However, a sub-group of patients with previous HSCT may be at increased risk of VOD. DF use in these patients is able to effect a clinical response and is safe in the majority of patients.

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