Management of Allogeneic Stem Cell Transplant Recipients with Hepatic Veno-Occlusive Disease

Alessandro Busca*

A.O.U. Città della Salute e della Scienza di Torino, Department of Oncology, SSD Trapianto allogenico di cellule staminali, Torino, Italy

Abstract: Hepatic veno-occlusive disease (VOD) or sinusoidal obstruction syndrome (SOS) is one the major limiting factor for the successful outcome of patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT), with a reported mortality rate of up to 50%. VOD/SOS is thought to result from an endothelial damage and occurs with a highly variable incidence ranging from 8% to 14%. Management of patients with VOD/SOS is based on both prevention and treatment, which rely on non-pharmacological approaches, for instance the control of additional risk factors, and pharmacologic treatments.

Herein we provide a review of the current understanding for the management of patients with VOD/SOS after allogeneic HSCT.

Keywords: Hepatic VOD/SOS, Endothelial damage, Transplant-related complications, Defibrotide.

INTRODUCTION

Bone marrow, peripheral blood stem cells and umbilical cord blood transplantation are medical procedures that are widely used to treat diseases once thought incurable. Nevertheless, the risk of transplant-related complications represents a major drawback in the allogeneic hematopoietic stem cell transplantation (HSCT) setting. Veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a potentially life-threatening complication of HSCT, occurring with a highly variable incidence, ranging from 8% to 14%.

Aim of present short review is to summarize the current understanding for the management of patients with VOD/SOS after allogeneic HSCT.

PATHOPHYSIOLOGY

VOD results from obliterative inflammation of the terminal hepatic venules in zone 3 of the hepatic acinus. VOD has been now renamed as SOS since damage to the sinusoidal endothelium is considered the primary event.

The pathophysiology of VOD involves the activation of and damage of Sinusoidal endothelial cells due to regimen-related toxicity inducing the subsequent release of toxic cytokines such as TNF-a and IL1b, the expression of adhesion molecules (ICAM-1 and VCAM-1) and release of heparanase eventually resulting in a further damage of the endothelium and gap formation which may facilitate the escape of red blood cells and leucocytes into the space of Disse leading to narrowing of the sinusoids.

DIAGNOSIS AND GRADING OF SEVERITY

The diagnosis of VOD/SOS is primarily based on clinical criteria, according to the Baltimore [1] and modified Seattle criteria [2]. The original definition of Seattle criteria has been modified including the bilirubin level and the percentage of weight gain (Table **1**). Nevertheless, it has now been recognized the presence of VOD/SOS with delayed onset as well as a defined clinical entity with less stringent diagnostic criteria and where hyperbilirubinemia should no longer be mandatory. According to these observations the EBMT endorsed the revised diagnostic criteria for VOD/SOS [3] (Table **1**). Taken as a whole, the classical triad of weight gain, hepatomegaly with right upper quadrant pain and elevated bilirubin may be variable present and may be incomplete or even delayed particularly in pediatric patients. Hence, the diagnosis of VOD, clinically based, still remains difficult in a consistent number of cases. Nevertheless, an accurate and prompt diagnosis of VOD/SOS is important for early initiation of appropriate therapy. In this respect the availability of imaging techniques, serological markers (*i.e*. PAI-1) and the use of hepatic biopsy may be considered as useful tools to further improve the diagnostic accuracy, in particular when the diagnosis is unclear. In fact, it is worth while recalling that several other conditions including GVHD,

*Address correspondence to this author at the A.O.U. Città della Salute e della Scienza di Torino, Department of Oncology, SSD Trapianto allogenico di cellule staminali, Torino, Italy; Tel: +39 011 6335359; Fax: +39 0116335759; E-mail: abusca@cittadellasalute.to.it

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Table. 1: Clinical Criteria for VOD/SOS

EBMT Criteria (3)		**Modified SEATTLE Criteria (2)**	**BALTIMORE Criteria (1)**
***Classical* VOD/SOS**	***Late Onset* VOD/SOS**		
First 21 days after HSCT	**>21 days after HSCT**	≥ 2 of the following criteria in the **first 20 days after HSCT**	During the **first 21 days after HSCT**, bilirubin must be > 2 mg/dL plus ≥ two of the following:
bilirubin must be > 2 mg/dL plus ≥ two of the following:	Classical VOD/SOS occurring >21 day after HSCT	Bilirubin > 2 mg/dL	hepatomegaly
Painful hepatomegaly	Or histologically proven VOD/SOS	Hepatomegaly or right upper quadrant pain	ascites
Weight gain >5%	Or ≥ 2 of the following: - Bilirubin > 2 mg/dL - Painful hepatomegaly - Weight gain >5% - ascites And hemadynamical and /or US evidence of VOD/SOS	Weight gain >2% from pre-HSCT weight	Weight gain >5% from pre-HSCT weight
Ascites			

Abbreviations: HSCT, hematopoietic stem cell transplantation; US, ultrasound

infections and drug toxicity mimicking hepatic VOD should be excluded.

The presence of multi-organ failure (MOF) is commonly used as a marker of severity of the disease, although several grading have been proposed [4-6]. Very recently, the new EBMT criteria for grading VOD/SOS severity have been published, based on bilirubin level and its rate of change, the value of transaminases, weight gain, renal function and the time elapsed from the first clinical symptoms [3].

RISK FACTORS

Recognition of potential risk factors for VOD/SOS is a key point for early diagnosis and prompt therapeutic intervention. A large number of risk factors have been identified for the development of VOD/SOS (Table **2**).

Table 2: Risk Factors for VOD/SOS After HSCT

Patient and disease-related risk factors
Older age
Performance score
Metabolic Syndrome
Genetic*
Leukemia in advance disease
Pediatric population with:
Osteopetrosis
Thalassemia
Hemophagocytic lymphohistiocytosis
Inborn errors of metabolism
Immunodeficiencies
Pre-transplant risk factors
Previous parenteral nutrition
Iron overload
Hepatic dysfunction: cirrhosis, fibrosis, active viral hepatitis
Transplant-related risk factors
Type of HSCT:
MUD
Mismatched
T-cell replete
Allogeneic > autologous
Conditioning regimen:
oral busulphan
12 Gy TBI
MAC>RIC
busulphan-endoxan
GVHD prophylaxis:
Sirolimus+CNI
Second HSCT
Previous/concomitant medications
Progestogens
Gentuzumab ozogamicin
Inotuzumab ozogamicin
Abdominal irradiation

Abbreviations: MUD, matched unrelated donor; TBI, total body irradiation; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; CNI, calcineurin inhibitors
*GSTM1-null genotype, C282Y allele, MTHFR 677CC/1298CC haplotype

MANAGEMENT OF VOD/SOS

Measures for the optimal management of patients with VOD/SOS encompass multiple steps aiming to prevent the occurrence of the disease or to treat an

already established VOD/SOS (Figure **1**). Prophylaxis tends to minimize any additional risk factors or administer medications which have been demonstrated to be useful in the prevention of VOD/SOS. The treatment of VOD/SOS is primarily based on supportive care and pharmacological treatment while only few reports have described the use of alternative therapies including transjugular intrahepatic portosystemic shunt (TIPS) or liver transplant.

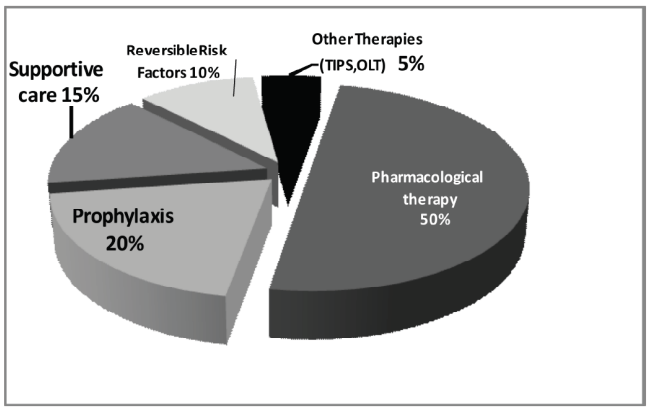

Figure 1: Management of VOD/SOS.

PROPHYLAXIS OF VOD/SOS

Preventive measures aiming to reduce the risk of VOD/SOS and the severity of the disease represent the first reasonable approach. Two options should be considered as the foremost preventive strategies. First, to minimize potential risk factors: unfortunately only few of these may be considered as reversible risk factors which may in turn be of clinical utility to be included as a prophylactic measure. The choice of preparative regimen and GVHD prophylaxis may be modified to mitigate the risk of VOD/SOS as well as iron overload may be reverted before the transplant and certainly, concomitant treatments with hepatotoxic drugs (*i.e*. progestogens) should be avoided whenever feasible.

Second, a pharmacological approach may be considered particularly in patients at high risk of VOD/SOS. Table **3** reports a summary of the studies evaluating the principal drugs used to prevent VOD/SOS.

Pentoxyfilline (PTX)

Associated with ciprofloxacin and prednisone has been investigated for prophylaxis of VOD due to the anti-TNF activity of this combination [7]. In fact, high TNF-alpha levels have been detected in transplant-associated microangiophaties including GVHD and VOD. However, the risk of VOD was not reduced with the administration of PTX while the combination was associated with a significant higher risk of bacteremia.

Antithrombin III (AT III)

Levels have been found low in patients with VOD/SOS. According to this observation Haussmann *et al*. designed a prospective study in pediatric patients where 91 patients were given pre-emptive AT III replacement in case of AT III activity below 70%; this group of patient was compared to an historical control group of 71 patients who did not receive any prophylactic treatment [8]. The incidence of VOD/SOS was not significantly different between the two groups, however it should be emphasized that all 14 patients in the study group who developed VOD/SOS, showed subnormal AT III levels 1 day prior to the diagnosis of VOD/SOS.

Heparin

Both unfractionated heparin (UFH) and low molecular weight heparin (LMWH) have been investigated as preventive strategies to decrease the risk of VOD/SOS, but only three studies are prospective and randomized [9-11]. The studies of Attal and Marsa-Vila included UFH (Table **3**), while LMWH has been evaluated by Or *et al* including 61 patients receiving allogeneic and autologous HSCT who were randomized to receive LMWH or placebo. Patients who were given LMWH had a reduced incidence of hepatomegaly and a reduced duration of elevated bilirubin (p 0.04 and p 0.01, respectively). A recent meta-analysis addressing the role of heparin as prevention of VOD/SOS identified 12 studies including 2782 HSCT recipients. The study showed a statistically non-significant beneficial effect of heparin, however the diversity of the studies might have precluded meaningful conclusions as witnessed by the extreme wide range of VOD/SOS incidence spanning from 2% up to 82% [12].

Prostaglandin E1 (PGE1)

The most recent study compared retrospectively the efficacy of PGE1 in a group of 40 patients with 10 patients who received heparin and 35 patients who did not receive any prophylaxis. No patients in the PGE1 and heparin group developed VOD as compared to an incidence of 14% of VOD/SOS in patients not receiving any drug [13].

Table 3: Summary of Pharmacological Measures for Prevention of VOD/SOS

	Study group (No. Patients)	Control group (No. Patients)		P value
Ferra', 1997 [7]	**PTX-CIPRO-PDN No. 37**	**No. 16**		
VOD	8%	25%		0.19
Bacteremia	62%	17%		0.05
Mucositis 3-4 grade	32%	56%		NS
GVHD III-IV	28%	14%		NS
Haussmann, 2006 [8]	**AT III - No. 91**	**No. 71**		
VOD	15%	18%		NS
Marsa-Vila, 1991 [11]	**UFH – No. 52**	**No. 46**		
VOD	7.7%	2.2%		NS
Attal, 1992 [9]	**UFH – N0.81**	**No. 80**		
VOD	2.5%	13.7%		0.01
Song, 2006 [13]	**PGE1 - No. 40**	**Heparin No. 10**	**No prophylaxis No. 35**	
VOD	0%	0%	14%	0.02
Ohashi, 2000 [31]	**UDCA – No. 67**	**No. 65**		
VOD	3%	18.5%		0.004
Ruutu, 2002 [32]	**UDCA – No. 123**	**No. 119**		
VOD, Jones criteria McDonald criteria	2% 11%	4% 12%		NS NS
GVHD III-IV	4%	14%		0.01
Chronic GVHD	47%	45%		NS
NRM at 1 year	19%	34%		0.01
Park, 2002 [33]	**UDCA+Heparin No. 82**	**Heparin No. 83**		
VOD	15.9%	19.3%		0.348
Median day of VOD onset	11	12		0.9
VOD after Allogeneic HSCT	34%	30%		0.702
Corbacioglu, Lancet 2012 [19]	**DFT - No. 180**	**No. 176**		
VOD by d30	12%	20%		0.04
Median time to diagnosis, days	17.5	14		0.5
VOD by donor type Allogeneic autologous	 8% 4%	 14% 6%		-
hemorrhage	22%	21%		0.8
TAM	3%	4%		0.75
GVHD II-IV	22%	37%		0.013

Abbreviations. PTX, Pentoxifylline; CIPRO, Ciprofloxacine; PDN, prednisone; AT III, antithrombin III; LMWH; low molecolar weight heparin; PGE1, Prostaglandin E1; UDCA, Ursodeoxycholic acid; NMR, nonrelapse mortality; DFT, Defibrotide; TAM, thrombotic microangiopathy.

Ursodeoxycholic Acid (UDCA)

Three prospective randomized trials addressed the role of UDCA for the prevention of VOD/SOS (Table **3**). A systematic review of the studies on the use of UDCA for the prevention of VOD/SOS has been published [14]. Overall, 6 studies including 824 patients have been analyzed. The review demonstrated that

prophylaxis with UDCA significantly attenuates the risk of VOD/SOS resulting in a lower TRM and a trend toward a lower rate of acute GVHD.

Defibrotide (DFT)

Is a mixture of oligonucleotides derived from depolymerization of cow lung or porcine intestinal mucosa. DFT was primarily investigated as an adenosine receptor agonist and only subsequent studies have shown its antithrombotic properties. Table **4** summarizes the main activities of DFT.

Table 4: Main Activities of Defibrotide (DFT)

(1) VASCULAR INTEGRITY	- Reduces vascular permeability - Reduces vascular inflammation - Promote angiogenesis
(2) ANTITHROMBOTIC and THROMBOLITIC properties	- Increasing levels of tPA - Increasing activity of plasmin - Reducing PAI-1 levels - Reducing platelet activating factor - Reducing thrombin
(3) ANTI-INFLAMMATORY effects	- Increases PGE2 and prostacyclin 2 - Reduces: IL-6 thromboxane A2 leukotriene B4 TNF ICAM-1
(4) Protective effect against GVHD	- Inhibits T-cell function (through activation of adenosine receptor) and proliferation - decreases TNF, IL-1, IL-2

Several studies have evaluated the efficacy and toxicity profile of DFT for prophylaxis of VOD/SOS in both adult and pediatric patients [15-18]. A phase 3 open-label prospective trial including 356 children who received autologous (n=108) or allogeneic (n=248) HSCT has been recently published [19]. Overall, 180 patients were allocated in the DFT group and 176 in the control group. DFT was administered at the dose of 25 mg/Kg/day from day 0 until day +30. Patients had one or more risk factors for VOD/SOS: (i) pre-existing liver disease, (ii) second myeloablative HSCT, (iii) leukemia in > 2^{nd} relapse, (iiii) preparative regimen including busulphan and melphalan, (iiiii) previous treatment with gemtuzumab ozogamicin and (iiiiii) diagnosis of lymphohistiocytosis, adrenoleukodystrophy or osteopetrosis. The results of the study demonstrated that 12% of the patients who received DFT developed VOD/SOS by day 30 post-HSCT, compared to 20% of the patients in the control group (p 0.04). Interestingly, in allogeneic HSCT recipients, the incidence and severity of acute GVHD were lower in the DFT group as compared to the control group (Table **3**).

Guidelines

In accordance to the findings of the Corbacioglu's study, the British guidelines recommend prophylaxis with DFT 6.25 mg/kg QID both in children (1A) and adults (2B) receiving allogeneic HSCT with the abovementioned six risk factors [20]. UDCA may considered as an alternative drug with a lower strength of recommendation (2C). PGE1, PTX and ATIII are not recommended due to lack of efficacy, while UFH and LMWH are not recommended due to the risk of bleeding. Similar recommendations have been proposed by the EBMT Group [21].

SUPPORTIVE CARE

An adequate supportive care may represent the first measure for VOD/SOS treatment even when the diagnosis is only suspected. The maintenance of a correct fluid balance along with the administration of diuretics for severe fluid overload re of extreme importance. Paracentesis should be considered to symptomatically improve the discomfort caused by ascites and to avoid a reduction in renal flow. Hemodyalisis/hemofiltration should be considered in case of uncontrolled fluid retention and renal failure. It is noteworthy recalling the importance of an early discussion with a specialist hepatology unit in order to evaluate alternative options for instance TIPS and liver transplantation.

PHARMACOLOGICAL TREATMENT OF VOD/SOS

Recombinant Human Tissue Plasminogen Activator (rh-TPA)

The largest retrospective study analyzed 42 patients with VOD/SOS who were treated with rh-TPA and heparin [22]. Patients received rh-TPA at a dose ranging from 5.4 to 120 mg i.v. over 2-4 days in association with heparin (1000 U as bolus dose followed by 150 U/Kg/day by continuous infusion for 10 days). Complete remission of VOD/SOS and day +100 overall survival (OS) have been reported in 29% and 24% of the patients respectively; severe bleeding episodes have been observed in 10 patients.

N-Acetylcysteine (NAC)

NAC is an antioxidant glutathione precursor that may reduce cell death mediated by oxidative stress.

NAC is commonly used as an antidote for the overdose of paracetamol hepatotoxicity and may provide protection from liver toxicity. One prospective randomized trial investigated the usefulness of NAC in allogeneic HSCT recipients [23]. Patients with bilirubin > 26 mmol/L and/or AST/ALT > 84 U/L were randomized to receive NAC 100 mg/Kg/day i.v. (n=72) or no treatment (n=88). Maximum bilirubin level and recovery of AST/ALT were similar in patients randomized to NAC or no treatment. The authors conclude that NAC does not improve liver toxicity in patients undergoing HSCT.

Methylpredisolone (MP)

One prospective study evaluated the safety and efficacy of MP in 48 patients with diagnosis of VOD/SOS. MP was administered at the dose of 0.5 mg/Kg BID for 14 days [24]. Response rate was 63%, however relevant treatment-related toxicities have been reported: 17% of the patients developed sepsis, 34% of the patients developed CMV infection and 10% of the patients presented with invasive fungal infections.

Defibrotide (DFT)

Table **5** reports a summary of the studies regarding the treatment of VOD/SOS with DFT.

The results of a phase 3 study investigating safety and efficacy of DFT in patients with VOD/SOS and multi-organ failure (MOF) have been recently published [25]. Overall 102 patients given DFT 25 mg/Kg/day were compared to 32 historical controls. Complete remission by day +100 was 25.5% and 12.5% respectively in the DFT and control group (p 0.0160), and OS by day +100 was 38% vs. 25% in the two groups (p 0.0109). Main treatment-related adverse events in the DFT group and control group included hypotension (respectively 39% vs. 50%), hematuria (respectively 10% and 16%), pulmonary alveolar hemorrhage (respectively 12% and 16%) and gastro-intestinal bleeding (respectively 8% and 9%).

One of the largest retrospective studies included 8341 patients selected from the Center for International Blood and Marrow Transplant Research (CIBMTR)

Table 5: Summary of the Studies Regarding Treatment of VOS/SOS with Defibrotide (DFT)

Reference	Population	Study	Treatment Option & Sample Size	Complete Remission (%)	Outcome (d+100 OS)	Toxicity (Tretment-Relted AEs)
Sucak, 2007 [34]	Adult	Retrospective	DFT 10-25 mg/Kg/d, n=14	**78%**	**78%**	-
Richardson, 2010 [28]	Adult & children	Prospective Randomized	DFT 25 mg/Kg, n=75	**46%**	**44%**	7%
			DFT 40 mg/Kg, n=74	**42%**	**39%**	10%
Corbacioglu, 2004 [35]	Children	Retrospective	DFT 40 mg/Kg, n=45	**76%**	**64%**	7% discontinution
Triplett, 2015 [27]	Adult & children	Prospective	Dose finding 10 mg/kg up to 110 mg/Kg (n=34)	**56%**	**44%**	Bleeding, hypotension
Corbacioglu, 2016 [36]	Adult & children	Retrospective	DFT 10-25-40-60-80 mg/Kg/d, n=710	**-**	**54%**	-
Richardson, 2016 [37]	Adult & children Acute Leukemia.	Retrospective	DFT 25 mg/Kg/d, n=756	**-**	**AML 45%** **ALL 43%**	AML 22% ALL 17%
Richardson, 2016 [25)]	Adult & children	Phase III study	DFT 25 mg/Kg/d, n=102	**25%**	**38%**	Hypotension: 39% GI bleeding: 8%
			Historical controls,n=32	**12%**	**25%**	Hypotension: 50% GI bleeding: 9%
Strouse, 2016 [26]	Adult & children	Retrospective	DFT vs Other treatments	**51% vs 29%**	**39% vs 30%**	-

database [26]. VOD/SOS and severe VOD/SOS defined as disease occurring in the setting of multi-organ failure, were identified in 3.2% and 1.2% of the patients respectively. Among patients with severe VOD/SOS, 41 were treated with DFT and 55 did not receive DFT. Patients in the DTF group were older, were more likely to have previous fungal infection and had higher proportion of organ impairment. Complete response of VOD/SOS at day+100 was 51% in the DFT group and 29% in the control group, while OS at day +100 was 39% and 30% in the two groups respectively. Interestingly, the incidence of grade II-IV and III-IV acute GVHD were 23% and 11% in the DFT group as compared to 38% and 29% in the control group. This finding combined with the data of Corbacioglu *et al.* [19] showing a lower incidence and severity of GVHD among patients who received DFT as prophylaxis for VOD/SOS, further strengthen the observation of a potential protective effect of DFT on GVHD, in accordance to the immunomodulatory effects of DFT which includes the inhibition of T-cell activity and proliferation, and reduction of TNF, IL-1, IL-2 levels (Table **4**).

The optimal dosage of DFT has been investigated in several studies. Triplett *et al* conducted a prospective trial evaluating escalating dosed of DFT from 10 mg/Kg up to 110 mg/Kg/day [27]. The dose of DFT could be safely escalated up to 100 mg/Kg/day without an increase in bleeding risk, however the efficacy of DFT at higher doses remains unclear. Richardson *et al*. published a randomized phase II dose-finding trial assessing the efficacy of DFT in allogeneic HSCT recipients with severe VOD/SOS [28]. Adult and pediatric patients were randomized to receive DFT at the dose of 25 mg/Kg/day (DFT25 group, n=75) or 40 mg/Kg/day (DFT40 group, n= 74). Overall, complete response was reported in 49% of the DFT25 patients and 43% of the DF40 patients (p 0.613), and the rates of complete responses were not significant different in a subgroup analysis of adult and pediatric patients. Similarly, OS at day +100 was not different in the DFT25 and DFT40 group, and treatment-related adverse events have been reported in 7% of the patients in the DFT25 group and 10% of the patients in the DFT40 group (p 0.563). In conclusion, DFT at the dose of 25 mg/Kg/dy demonstrated to be effective in treating severe VOD/SOS as the dose of 40 mg/Kg/day with low treatment-related toxicity.

The optimal time to initiate the treatment of VOD/SOS with DFT represents a critical issue. Several studies suggest the earlier intervention may be associated with a more favorable outcome [29]. Sixty % of patients were alive when defibrotide was started within 2 days from the onset of symptoms as compared with 14% when treatment was delayed and started after 7 days [30].

Guidelines

The British guidelines recommend the use of DFT for the treatment of adults and pediatric patients with VOD/SOS (1B) [20]. By contrast, rh-TPA and NAC are not routinely recommended, due to the risk of hemorrhage (rh-TPA) and lack of efficacy (NAC). MP may be considered with caution due to the risk of severe infections.

CONCLUSION

The management of VOD/SOS must initiate with timely diagnosis of the disease, including the recognition of early signs and symptoms and the use of serological markers, imaging and even invasive procedures when the diagnosis in unclear and requires the exclusion of other confounding conditions (*i.e*. GVHD, infections, drug toxicity). Preventive measures include the recognition of risk factors which might be reverted and pharmacological interventions, for instance the administration of UDCA and DFT in high risk patients. The treatment of an overt VOD/SOS includes an adequate supportive care and the administration of drugs with proven efficacy such as DFT. It should be emphasized that the treatment of VOD/SOS with DFT is associated with better outcome particularly when DFT is administered within the first 2 days from the diagnosis.

DISCLOSURES

A.B. has received honoraria from Gilead Sciences, Merck, Pfizer Pharmaceuticals and Jazz Pharmaceuticals; he has been speaker for Gilead Sciences, Merck, Pfizer Pharmaceuticals, Astellas Pharma, and Basilea.

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