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Section XVII: Transplant Complications

Hepatic Veno-Occlusive Disease after Hematopoietic Stem Cell Transplantation: Novel Insights to Pathogenesis, Current Status of Treatment, and Future Directions

P.G. Richardson*, V.T. Ho, C. Cutler, B. Glotzbecker, J.H. Antin, R. Soiffer

Division of Hematologic Malignancy, Dana-Farber Cancer Institute, Boston, Massachusetts

INTRODUCTION

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome, is a potentially life-threatening complication after hematopoietic stem cell transplantation (HSCT). VOD affects both adult and pediatric populations alike, with a higher incidence in the allogeneic setting [1]. Disease onset is typically within the first 30 days after HSCT [1], although later occurrence has been reported [2]. It is characterized by clinical features such as hepatomegaly, jaundice, weight gain, and ascites [3,4]. VOD is reported to occur in 8% to 14% of patients after HSCT [3], although incidence rates may be as high as 60% in higher-risk patients (such as those with underlying liver disease and certain specific drug exposures, including gemtuzumab, ozogamicin, and sirolimus) and depending on the diagnostic criteria used [3,4]. Severe VOD (sVOD) is typically associated with multiorgan failure (MOF) and high mortality rates (>80%) [3,4]. Even among patients with moderate VOD, the mortality rate is still estimated at approximately 20% [5].

PATHOGENESIS

VOD is thought to be triggered by activation and damage to the sinusoidal endothelial cells in zone 3 of the hepatic acinus due to conditioning regimen–mediated injury [6]. Activated sinusoidal endothelial cells express cytokines (eg, tumor necrosis factor-α and interleukin-1β) and adhesion molecules (eg, intracellular adhesion molecule 1 [ICAM-1] and vascular cell adhesion protein 1 [VCAM-1]), resulting in activation of proinflammatory pathways that further damage the endothelium [7]. This leads to the loss of endothelial wall fenestrae and formation of gaps between sinusoidal endothelial cells [2]. Consequently, red blood cells, leukocytes, and cellular debris extravasate into the space of Disse, causing progressive extraluminal compressive narrowing of the sinusoids [2,7,8] and dissection of the endothelial cell lining cells, which could further embolize downstream and occlude the sinusoid [2]. In addition, injury to the sinusoidal endothelial cells of the sinusoids is also associated with a procoagulant and hypofibrinolytic state that contributes further to fibrin deposition, clot formation in situ, and narrowing of the sinusoids [6-8]. Together, these effects reduce hepatic venous outflow, leading to postsinusoidal hypertension, central venular-occlusion, hepatic enlargement with capsular distension, and, in more severe cases, portal venous flow reversal and hepatorenal syndrome, leading to MOF and death [2].

DIAGNOSIS AND PROGNOSIS OF VOD

The diagnosis of VOD is often made based on clinical criteria; the Seattle criteria stipulate that at least two or more clinical features, including jaundice, painful hepatomegaly or ascites, and/or unexplained weight gain, must be evident within 30 days of transplantation [8,9]. Conversely, the more rigorous Baltimore criteria specify an elevated bilirubin level of at least 2.0 mg/dL and two or more of the following characteristics: hepatomegaly, ascites, or at least 5% weight gain by day +21 post-HSCT, with the Baltimore criteria validated according to both histopathologic features and outcome [8,10].

VOD presents with a wide spectrum of severity and is conventionally divided into mild, moderate, and severe disease [11]. Mild VOD is considered disease that meets diagnostic criteria, does not require specific treatment for fluid excess or medication for hepatic pain, and has a self-limiting course. Moderate VOD is disease with evidence of liver injury that requires active treatment for fluid excess or medication for hepatic pain but that usually resolves completely. sVOD is defined as disease that is usually associated with MOF, severe hyperbilirubinemia with rapid weight gain, and typically leads to death [12]. Although several biomarkers of endothelial injury, such as plasminogen activator inhibitor type-1, have been shown to be elevated in patients with VOD [13,14], no laboratory marker has been standardized or validated as a diagnostic indication of VOD. Based on retrospective analyses, the presence of MOF has emerged as the best clinical marker for VOD severity to date. The Bearman model, which estimates the risk of developing sVOD based on bilirubin level, percentage weight gain, and a designated time frame from HSCT, has also demonstrated utility for predicting VOD severity. However, because the Bearman model was developed in a cohort of patients who developed VOD within 17 days of HSCT after specific conditioning regimens, its general applicability to other conditioning regimens and later time frames post-HSCT is limited [3,4,15]. In this context, sensitive and specific biomarker assays are needed that could guide disease prognostication and management, with some candidate markers under study but none yet defined.

TREATMENT OPTIONS AND PATIENT MANAGEMENT

Current management of VOD consists primarily of supportive care, with a focus toward fluid management, adequate oxygenation and transfusional support to minimize

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* Correspondence and reprint requests: Dr. P.G. Richardson, Dana-Farber Cancer Institute, Division of Hematologic Malignancy, 44 Binney St., Boston, MA 02115.

E-mail address: Paul_Richardson@dfci.harvard.edu (P.G. Richardson).

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ischemic liver injury, and avoidance of hepato/nephrotoxins [12,16]. The use of tissue plasminogen activator with or without heparin has been evaluated in a number of studies and small case series. However, results have generally been disappointing; although about one-third of patients show improvement in their VOD with thrombolytic therapy, life-threatening hemorrhages are common, and no survival advantage is apparent [12].

Although no agents to date have been approved for the treatment of VOD either in the United States or the European Union, the investigational drug defibrotide (DF) has shown the most promising results in clinical trials to date. DF is a polydisperse oligonucleotide with fibrinolytic properties (but no significant systemic anticoagulation) that has also demonstrated protective effects on micro- and macrovascular endothelium. The use of DF for the treatment of VOD is supported by a number of large clinical trials showing that DF improves both complete response (CR) and survival. These include a large multicenter, prospective, randomized phase II study that established an effective DF dose of 25 mg/kg/day in divided doses administered intravenously every 6 hours [16].

Promising studies using historical controls [17,18] and, more recently, a multicenter, randomized, prospectively controlled trial in children [5] demonstrated the efficacy of DF for prophylaxis of VOD. As such, orphan drug status has been granted for DF for the treatment and prophylaxis of VOD by both the European Medicines Agency [19,20] and US Food and Drug Administration [21].

The use of DF for the treatment of VOD is further supported by a large number of clinical trials showing that DF improves both CR and survival. The efficacy of DF for the treatment of sVOD was first demonstrated in a retrospective dose escalation study of 19 patients with sVOD and MOF performed in the United States that showed complete resolution of VOD in 8 patients (42%), 6 of whom survived for longer than 100 days with no significant bleeding observed [22]. A number of trials have subsequently confirmed the efficacy of DF in this setting, including a similar European multicenter compassionate-use study, which treated 40 patients and demonstrated a 55% CR rate, with 43% patients alive after 100 days [23]. Importantly, a recent pivotal phase III, historically controlled trial of DF in 102 patients with sVOD/MOF showed a superior 100-day CR rate in the DF group compared with historical controls (24% vs 9%, respectively; adjusted $P = .015$) and a lower 100-day mortality rate with DF compared with historical controls (62% vs 75%, respectively; adjusted $P = .051$) [24]. Recognizing VOD with MOF as a life-threatening condition with no other effective treatment options, the US Food and Drug Administration permitted access to DF in the United States through an investigational new drug compassionate-use treatment protocol in December 2007. An interim analysis of 269 patients enrolled between December 2007 and March 2011 at 67 US centers revealed that 32% of patients achieved a CR at day-100 post-HSCT, with an overall day-100 survival of 50% [25]. From this protocol, 134 patients would have met entry criteria for the pivotal phase III trial, and comparison with the phase III-derived historical controls showed a statistically improved outcome in CR (30% vs 9%; $P = .0006$) and day-100 survival (46% vs 25%; $P = .006$) [25].

As mentioned above, encouraging results observed with DF in treatment trials have also led to further investigation of its use as prophylaxis for VOD after HSCT. A number of prospective historically controlled trials have reported benefits with DF prophylaxis in children at high risk of developing VOD [26-29]. These early studies are also strongly supported by the recent prospective, multicenter, phase II/III studies in the European Union [5]. This trial randomized 360 children (<18 years) undergoing myeloablative HSCT to receive either prophylactic DF from conditioning to 30 days post-HSCT or no prophylaxis (control group). In the intent-to-treat analysis (n = 356), there was a 40% reduction in VOD by day-30 post-HSCT in patients receiving prophylactic DF compared with the control group (12% vs 20%; $P = .051$). Another important observation was that the mortality rate at 100 days was 4 times higher in patients who developed VOD than in those without VOD (25% vs 6%; $P < .0001$). It is also noteworthy that the incidence of acute graft-versus-host disease, which was a secondary endpoint in the trial, was also significantly lower in the DF prophylaxis arm, an observation consistent with similar findings in treatment studies, where rates of graft-versus-host disease were remarkably low.

To date, DF has been used in more than 240 transplantation centers across 33 countries as a result of a large compassionate-use program and the ongoing named patient programs. Based on an overall experience in more than 1,800 patients, DF continues to demonstrate remarkable safety and tolerability despite a very ill patient population, with manageable toxicities and low rates of attributable hemorrhage [30].

FUTURE DIRECTIONS

Despite the promising results from clinical trials with DF as treatment and prevention of VOD, day-100 mortality from sVOD remains unacceptably high. Recent observations have shown that delayed initiation of treatment is associated with a worse outcome, highlighting the importance of early intervention once a VOD diagnosis is established [25]. The role of DF in the VOD treatment paradigm may, in fact, be optimized with its use in early disease or as prophylaxis. Additional prospective studies in VOD prevention are now planned in adult HSCT populations and specific high-risk settings. Elevations of von Willebrand factor, thrombomodulin, E-selectin, and soluble ICAM-1 before and early after allogeneic transplantation may be useful in predicting VOD in patients receiving sirolimus [31] as graft-versus-host disease prophylaxis and could lead to pre-emptive treatment or prevention trials based on these and other biomarkers [1]. Finally, additional therapies, such as low-molecular-weight heparin, *N*-acetyl cysteine, antithrombin III, and other novel antithrombotics, may warrant further investigation in combination with DF [1,32].

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