HEPATIC VENO-OCCLUSIVE DISEASE AFTER BONE MARROW TRANSPLANTATION

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ABSTRACT

In the first few weeks after bone marrow transplantation, a clinical syndrome characterized by hepatomegaly, jaundice, and fluid retention develops in 10 to 70% of patients. This syndrome is due to damage to endothelial cells, sinusoids, and hepatocytes in zone 3 of the liver acinus. The proximate cause of the damage is cytoreductive therapy. This syndrome, often called veno-occlusive disease of the liver, can vary in severity from mild reversible disease to fatal disease associated with multiorgan failure.

Key Words: Hepatic veno-occlusive disease, Bone marrow transplantation, Cytoreductive therapy.

INTRODUCTION

Jaundice in the first several weeks after bone marrow transplantation (BMT) is most often secondary to liver toxicity following cytoreductive therapy (veno-occlusive disease; VOD), liver injury caused by other medications, and the cholestatic liver disease associated with sepsis. Acute Graft Versus Host Disease (GVHD) affecting the liver presents after day 15. Fungal infections of the liver are related to poor graft function and granulocytopenia. Viral hepatitis usually occurs after day 40.

VOD of the liver is a hepatotoxic lesion involving progressive and concentric non-thrombotic obstruction of the small intrahepatic venules and damage to the surrounding centrilobular hepatocytes, and sinusoids (1). It was initially described in Jamaicans who had drunk teas made from plants containing pyrrolizidine (seneico) alkaloids (2). To day it occurs principally as a complication of chemotherapy and radiation therapy, especially after BMT. The first case of VOD after BMT was reported in 1979 (3). Since then, BMT has proved to be the main cause of VOD and this disease is considered to be one of the most common life threatening complication of preparative-regimen-related toxicity for BMT (4,5). In this review, we focused on the pathogenesis, diagnosis, risk factors and management of VOD in the setting of BMT.

Pathology

Most pathologic descriptions of human VOD come from human autopsy material. In the earliest recognizable histologic lesions of VOD, the lumen of small hepatic venules is narrowed by an edematous concentric subendothelial zone containing fragmented red cells, debris and fibrillar material (1,6,7). The surrounding sinusoids are congested and the intervening hepatocytes in centrilobular zone are pale to frankly necrotic. When patients are evaluated several weeks after the onset of the disease, the affected venules become partially or completely obliterated by subendothelial collagen fibers and foamy cells containing lipofuscin, bile and hemosiderin pigments. Surrounding hepatocytes are atrophic and the sinusoids are dilated and often filled with atrophic material (4,8). When VOD is examined by ultrastructural and immunohistochemical techniques, deposits of fibrinogen and Factor VIII within the adventitial and subendothelial zone of the affected venules are detected (9,10).

Other lesions reported with the VOD syndrome:

Several clinicopathologic studies based on necropsy material of marrow transplant recipients indicate that a clinical syndrome, similar, if not identical, to that produced by VOD lesions may be observed with several other zone 3 histologic alterations, even in the absence of VOD lesions (11,12). VOD must be distinguished from these minor forms of liver toxicity following chemoradiation therapy. These lesions are zone 3 hepatocyte necrosis, phlebosclerosis and zone 3 sinusoidal fibrosis (4,8). The diagnosis of VOD is not usually accepted unless significant changes in the central veins exist (1,13).

Nodular regenerative hyperplasia (NRH) is a type of non-cirrhotic portal hypertension that consists of hepatocellular nodules distributed throughout the liver in the absence of fibrous septae between the nodules (14). In 1989, Snover et al described high incidence of NRH among BMT patients. However, this was not confirmed in a recent analysis by Shulman et al (15). These authors observed only 8% NRH and this was not related with early liver toxicity following cytoreductive therapy.

Pathogenesis

Conditioning chemoradiotherapy has been suggested as the proximate cause of VOD after BMT. However the genesis of this disease is probably multifactorial. Because endothelial cells are particularly sensitive to chemoradiotherapy, one hypothesis proposes that venular and sinusoidal endothelial injury during conditioning therapy results in local activation of the clotting cascade, first occluding sinusoidal pores that drain into venules, causing postsinusoidal obstruction to venous blood flow (4,10). Shulman et al showed that in early stages of VOD there is a deposition of fibrin and Factor VIII first within the adventitial zone and then into the subendothelial zone of the affected venules (10). Other findings observed by other authors such as: (1) a modification in von Willebrand factor and serum angiotensin converting enzyme levels, suggesting an endothelial injury; (2) a decrease in the natural anticoagulant concentrations such as protein C, protein S, and antithrombin III and (3) an increase in factor IX, fibrinogen and hyaluronic acid and a decrease in factor VII levels. These findings suggest that the endothelial damage activates the coagulation process favoring clot formation over natural anticoagulation (16,17).

These is also a role of cytokines in the genesis of VOD. The best known are tumor necrosis factor-alpha (TNF-alpha), and interleukin 1 and 2 (IL-1, IL-2) (18,19). The major source for TNF-alpha is reticuloendothelial cells (monocytes, macrophages, Kupffer cells), but it can also be synthesized in the endothelium. TNF-alpha causes downregulation of thrombomodulin, plasminogen, prostaglandin E1 and E2, and protein S and upregulation of cellular adhesion molecules, platelet derived growth factor, and endothelial derived coagulation factors V and VIII. It also causes local synthesis of tissue factor. TNF-alpha also produces cytotoxicity thought to be mediated by free oxygen radicals (20). The hepatic sinusoidal endothelium expresses CD14 which serves as a receptor for lipopolisaccharide (21), the most potent stimulus for the production of TNF-alpha (20). However other cytokines such as IL-1 and IL-2 and interferons can induce TNF-alpha. Related pretransplant events such as alloimmune reactions, septicemia, and congestive heart failure can cause the release of IL-1 and TNF-alpha which would subsequently increase the expression of tissue factor on tissues and initiate the process of coagulation (22).

High and sustained levels of cyclosporine (CSP) given prior to cyclophosphamide (CY) conditioning in patients transplanted for severe aplastic anemia produced the occurrence of VOD in 2 of 10 patients (22). In this setting, the authors hypothesized that CSP may have rendered the centrilobuler hepatocytes more susceptible to the potentially toxic effects of activated CY metabolites. CSP treatment also promotes hemostasis and retards thrombolysis by increasing platelet aggregation, reducing endothelial prostaglandin and increasing endothelial thromboplastin (23,24).

The characteristic centrilobular location of VOD seems to be the consequence of peculiar drug metabolism in the liver. Most drugs require conversion to water-soluble metabolites for their elimination. This conversion is accomplished by cytochrome P-450 and by conjugating enzymes. The toxicity of the drugs is limited by several protective mechanisms, such as transformation into stable metabolites by glutathion and glutathion dependent enzymes. Centrilobular hepatocytes are very rich in cytochrome P-450 and poor in glutathione, this makes them main target for toxic metabolites (25). So, when a drug that is a source of toxic metabolites, like CY, is administered simultaneously with agents which reduce glutathione, such as radiation, busulfan or BCNU, there is a high probability of hepatocyte and sinusoidal endothelium damage in zone 3 of the acinus (4,26).

Clinical features

According to the review of the literature, the incidence of VOD is 0 to 70% (27-30). This is probably due to the different incidence of risk factors in the different series.

Clinical features of hepatic VOD are presented in Table I. Usually a weight gain exceeding 2% of the baseline which is non attributable to a fluid overload is the first symptom of VOD (31-33). This is due to a renal retention of sodium and water, and appears in 90-95% of patients who develop VOD around day 6 to 8 after BMT. Two to three days later, a hyperbilirubinemia of variable intensity is observed in 98% of the cases. Most patients develop ascites to a variable degree. Around day 12 after BMT, 50-75% of patients develop abdominal pain in the right upper quadrant. A large tender liver is present in most of them. Many patients with VOD show refractoriness to platelet transfusions (4,31,33-35). More than 50% of VOD cases develop mild to severe renal failure (36).

Table I: Clinical Features of Hepatic VOD

- **Painful hepatomegaly**
- **Sudden weight gain**
- **Jaundice**
- **Edema**
- **Ascites**

The onset of VOD has been remarkably consistent in different series with most cases presenting between the second and third week post marrow infusion. However, when marrow transplant recipients are prospectively monitored, the onset of symptoms and signs of liver toxicity was appreciated even earlier with some features presenting during conditioning therapy even before the infusion of donor marrow (37).

Conversely, VOD developing more than 30 days after BMT has also been reported (33).

Patient outcome

VOD improves in 50 to 80% of cases, 17 to 25 days after onset (5,31,32,38,39). Two third of patients who die have multi-organ failure making it difficult to know what is the main cause of death (40). The remaining patients do not recover their liver function, dying later from other complications. There is also a high frequency of interstitial pneumonia, and other lung disturbances among VOD patients (40,41).

The clinical data that best correlate with the patients outcome are the amount of weight gain and the bilirubin concentration (32). Using these data, Bearman et al developed a statistical model to develop outcome (42). Pressure gradient between wedged and free hepatic venous pressures (HVPG) seems also to be helpful in predicting outcome. In a recent analysis, it was observed that all patients with a HVPG higher than 13 mmHG died (13).

Risk factors

Epidemiological studies have implicated many factors in the pathogenesis of VOD, the most important of which is the conditioning regimen itself. The incidence of severe VOD is higher following conditioning with CY and total body irradiation (TBI) when the dose of TBI is greater than 10-12 Gy (43). The schedule of delivery of TBI does not seem to influence the incidence of severe VOD, but some authors suggest that there is more VOD when TBI is delivered at higher dose rates (44), and less VOD with lower dose rates (45,46). The potential risk factors for VOD of the liver after BMT are demonstrated in Table II.

Table II: Potential Risk Factors for VOD of the Liver After Marrow Transplantafion

Pretransplant Factors:

Hepatitis [31, 49, 59]
Medications (vancomycin [37], acyclovir [37], amphotericin B [61])
Sex (female>male [60,6], no effect [1,47])
Age (Increased risk, Age>10 [62], > 15[47], no effect [31, 60])
Remission / relapse status (Increased in relapse [31,63], no effect [39])
CMV serology (Increased risk with positive serology [54])

Transplant Decisions:
Dose of conditioning (Increased with more intensive regimens [39])
Type of conditioning (Increased with the use of CY, TBI, Busulfan, Etoposide [39, 63, 64])
Type of marrow graft (Increased with allogeneic vs autologous [64,65], no change [39])
Degree of allogeneic match (Increased in mismatched or unrelated allogeneic recipients [39])

Clinical Course Factors:
Post-transplant GVHD prophylaxis (Increased risk with CSP/methotrexate [66]
no change [39,64,65])

Diagnosis

The diagnosis of VOD can be established with accuracy only by a histological examination of the liver. However, the high risk of bleeding in patients who are usually refractory to platelet transfusions preclude a percutaneous liver biopsy. Furthermore, this technique shows a high rate of false negative sampling probably due to patchy nature of VOD (1,8). For these reasons, the diagnosis of VOD is usually established on clinical grounds. Most transplant teams worldwide apply the clinical criteria proposed by the Seattle and Baltimore groups (Table III). (31,47). According to the authors, the accuracy of such clinical criteria is 89% and 95% respectively. The reliability of these clinical criteria was later assessed by means of transjugular liver study (TLS) (35). The specificity of VOD criteria established by Seattle and Baltimore was found to be 92%, but the sensitivity was relatively low.

VOD diagnosis is difficult to establish clinically when only some of the clinical criteria are present, or the timing of events is not typical, or there are clinical data suggesting another cause for the liver disturbance. In these cases, TLS has been recommended as a therapeutical approach which is safe and allows suitable liver samples to be obtained with a low incidence of false negative results (13,35). In addition, it permits the measurement of HVPG.

Ultrasonography of the abdomen can help to establish the diagnosis of VOD (48,49). Ascites, hepatomegaly, failure to visualize hepatic veins and gallbladder wall thickening have been reported as nonspecitic findings in association with VOD.

Prophylaxis

Prevention of clot formation is a prophylactic approach for VOD. The effect of low-dose heparin in decreasing the incidence of VOD after BMT have initially been reported (50,51). Later, Bearman found that the effect of heparin on VOD was very little (52). However in a subsequent prospective randomized trial, it was shown that continuonus infusion of low-dose heparin was highly effective in preventing VOD without risk of bleeding (53).

Prostaglandin E1 (PGE1) was shown to be useful in the prevention of VOD after BMT (54). It exerts several pharmacological effects like vasodilatation, inhibition of platelet aggregation, activation of the fibrinolytic system, stimulation of the release of endogenous tissue plasminogen activator and acceleration of thrombolysis (55). Baerman et al, on the other hand, could not reproduce these effects in patients with high risk for VOD and observed important toxicity, particularly among patients receiving CSP (56).

In a non randomized study in BMT patients, pentoxifyline (PTX) reduced the incidence of VOD, renal insufficiency and acute graft versus host disease. PTX modulates TNF-alpha production and stimulates vascular endothelial production of non-inflammatory prostaglandins (57).

Table III: Clinical Criteria for VOD Diagnosis

I) Seattle criteria:

Presence of at least two of the following features within 30 days after transplantation:

1) Jaundice
2) Hepatomegaly and right upper quadrant pain
3) Ascites and/or unexplained weight gain

II) Baltimore criteria:

Hyperbilirubinemia ≥ 2mg/dL within 21 days after transplantation,
and at least, two of the following data:

1) Hepatomegaly, usually painful
2) Ascites
3) Weight gain > 5% from baseline

Treatment

The treatment of VOD is primarily supportive, with careful management of fluid overload and its attendant complications. Restriction of dietary and parenteral sodium and the use of diuretics will reduce fluid retention but carries the risk to generate an intravascular volume depletion. This can generate renal failure in patients usually receiving other nephrotoxic drugs. Thus, the goal should be to maintain intravascular volume and renal perfusion avoiding extravascular fluid accumulation. Red cells, albumin and colloid infusions can help to maintain intravascular volume (4,5). When fluid accumulation and renal failure cannot be controlled, hemodialysis will be required (38). Paracentesis may be considered when ascites becomes uncomfortable or limits respiration. Encephalopathy must be treated with protein restriction and oral lactulose.

PGE1 was used successfully to improve the venular occlusion in several cases (58). Recombinant tissue plasminogen activator (rt-PA) has a high affinity for fibrin bound plasminogen resulting in an efficent activation of plasmin on fibrin clots with subsequent clot lysis. It was used safely and effectively in VOD treatment (59).

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