Background and Objective. The veno-occlusive disease of the liver (VOD) is a disorder caused by the non-thrombotic occlusion of the central veins of hepatic lobules. The clinical features are similar to those of intrahepatic portal hypertension (unexplained weight gain, ascites, painful hepatomegaly, jaundice). In the past, this disease was rather infrequent and was linked to the absorption of toxic agents, liver irradiation or chemotherapy. However, the intensification of treatment protocols before hematopoietic stem cell transplants has considerably increased its incidence. The strategies used for its prevention and treatment remain limited in efficacy. The present review was undertaken in order to assess progress in the diagnosis and management of this severe complication in stem cell transplantation.

Information Sources. The method used for preparing this review was an examination of 250 relevant articles or abstracts published in journals covered by Medline.

State of Art. Despite the progress made toward the understanding of its physiopathology and the identification of its risk factors, VOD is still one of the leading causes of morbidity and mortality during the first two months post-BMT, and therefore often constitutes a limitation for the further increment of the dose of antineoplastic drugs. This may be explained by the difficulty in making an early diagnosis of this problem, at a time when therapeutic intervention may be more effective, and, on the other hand, the lack of a well-established prevention and treatment approach for patients with VOD.

Perspectives and Conclusions. New diagnostic procedures, such as laparoscopic liver biopsy, and new therapeutic approaches, such as transjugular intrahepatic portosystemic shunting (TIPS) or defibrotide, are now being evaluated. However, additional studies will be needed to determine the most appropriate therapy for each VOD patient depending on the severity of the disease.

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Key words: stem cell transplantation, veno-occlusive disease, liver complications, anticoagulation

The veno-occlusive disease of the liver (VOD) results from a hepatotoxic lesion causing the obstruction of small intrahepatic venules, hence leading to lesions in the central zone hepatocytes and surrounding sinusoids. Although the disease was first described in some Jamaicans who habitually consumed local herb infusions containing pyrrolizidine alkaloids (senecio), nowadays VOD is above all a serious complication of bone marrow transplants (BMT). Its incidence varies considerably from 3% in pediatric centers that perform allogeneic transplants in children with thalassemia major, to more than 65% in centers that carry out bone marrow transplants in cases of advanced hematological disorders. However, the incidence of VOD varies among these centers, depending on their capacity to diagnose early and mild VOD. The Seattle and Baltimore groups have set up similar clinical diagnostic criteria for VOD (Table 1). Patients who meet modified Seattle criteria are retrospectively classified for severity in three groups (mild, moderate and severe VOD) based on their outcome (Table 2). In a cohort study of 355 patients, mild, moderate and severe VOD occurred respectively in 12%, 26% and 15% of the patients, and their mortality rates before day 100 were 9%, 23% and 98%, respectively. In this article, we will review the pathophysiology and various risk factors of this disease, describe its clinical, biological and anatomical aspects, and present options for its prevention and treatment.

Pathophysiology

Although the exact sequence of events leading to the clinical manifestations of VOD is still debated, the earliest event seems to be damage to the hepatocellular venular and sinusoidal endothelium, which locally induces a hypercoagulable state by activating the coagulation cascade and favoring clot formation over natural anticoagulation. Consequently, the venular and sinusoidal lumen is reduced due to an edematous concentric subendothelial zone con-
containing fragmented red cells, debris and fibrillar material, thus inducing partial to complete fibrotic obliteration of the venular lamina. Systemic abnormalities of coagulation proteins have been observed, either before conditioning in patients who will later develop VOD or after high-dose chemo- or radiotherapy. The main issue regarding these data is discovering whether these coagulation parameters are involved in the pathogenesis of VOD or if they are merely consequences of the disease. Several cytokines, such as TNF-α, IL-1 or TGF-β have been implicated on the basis of their known effects on endothelial cells and because of their elevated levels in patients before the onset of hepatic dysfunction associated with VOD. Although endothelial cells appear to be the primary target of events leading to VOD, hepatocytes also play a critical role. Centrilobular (zone 3) hepatocytes contain cytochrome P 450 enzymes that metabolize many of the chemotherapeutic agents used in conditioning regimens for BMT. Some drugs are transformed into toxic metabolites and then converted into stable metabolites by glutathione and glutathione-dependent enzymes that are present in only low concentration in centrilobular hepatocytes. Thus, when a drug that potentially gives rise to toxic metabolites is administered together with agents that reduce glutathione, there is a high probability of centrilobular hepatocyte injury and sinusoidal damage.

Risk factors for VOD

The occurrence of VOD is linked to a number of factors among which we can distinguish pre-transplant risk factors, risk factors associated with the conditioning regimen, and risk factors linked to the type of transplant.

Pre-transplant risk factors

The following risk factors are currently considered as being significantly associated with VOD: elevated transaminase levels before the beginning of the conditioning regimen; treatment for viral or bacterial infections at the beginning of the conditioning regimen; liver metastases or previous liver irradiation. Prior cumulative exposure to high doses of cytotoxic agents may contribute to these risks. Thus, a second marrow transplant preceded by a second conditioning treatment is often complicated by VOD. The contribution of the hepatitis C virus (HCV) to VOD is controversial. One study suggested that patients with liver disease caused by HCV infection are at a high risk of developing lethal VOD after BMT, but another report in a selected and homogeneous population did not confirm the association.

Risk factors related to the conditioning regimen

Nearly all preparative regimens before a hematopoietic stem cell transplant can cause VOD, particularly the most intensive ones. Nevertheless, some conditioning protocols seem to be more toxic than others. For instance, the association of cyclophosphamide and busulfan has been shown to cause VOD more than the association of cyclophosphamide and total body irradiation. However, some recent reports do not show such an association. The technique of total body irradiation administered may also be important since fractionating the dose could significantly reduce the risk of VOD in one study, but not in another. The total

Table 1. Clinical criteria for the diagnosis of VOD.

1) Seattle criteria (see ref. #5)
   Presence, before day 30 after transplant, of at least two of the following features:
   1. jaundice
   2. hepatomegaly and right upper quadrant pain
   3. ascites and/or unexplained weight gain

2) Baltimore criteria (see ref. #6)
   Hyperbilirubinemia ≥ 2 mg/dL (34.2 µmol/L) before day 21 after transplant and, at least, two of the following features:
   1. hepatomegaly (usually painful)
   2. ascites
   3. weight gain greater than 5% from baseline

3) Modified Seattle criteria (see refs. #6, 7)
   Occurrence of two of the following events within 20 days of transplantation:
   1. hyperbilirubinemia (total serum bilirubin > 2 mg/dL)
   2. hepatomegaly or right upper quadrant pain of liver origin
   3. unexplained weight gain (> 2% of baseline body weight) because of fluid accumulation.

Table 2. Classification of VOD according to its severity.

1) Mild VOD
   Patients have mild VOD if:
   1. they show no adverse effect from liver disease
   2. they require no treatment for VOD
   3. their illness is self limited

2) Moderate VOD
   Patients have moderate VOD if:
   1. they have an adverse effect from liver disease
   2. they require treatment for VOD (such as diuretics for fluid retention or medication to relieve pain from hepatomegaly)

2) Severe VOD
   Patients have severe VOD if:
   1. their VOD does not resolve before day 100
   2. they die of VOD
dose of radiation received by the patient is also correlated with VOD. The liver toxicity of busulfan clearly appears to be related to its pharmacokinetics: Grochow et al. originally correlated VOD with increased mean busulfan area under the curve vs. time (AUC) (>2012 µmol/min/L). A later prospective study by the same group confirmed an increased occurrence of VOD with AUC > 1500 µmol/min/L, and showed that adaptation of the dose according to the AUC significantly reduced the risk of VOD. However, one study was unable to correlate the risk of VOD with Busulfan pharmacokinetic parameters, and two additional papers reported that the adjustment of the dose according to the AUC failed to reduce VOD frequency.

Type of transplant
Contrary to what is commonly believed, multivariate analyses have shown that the incidence of VOD after allogeneic BMT is not higher than its incidence after autologous BMT. Nevertheless, the relative risk of severe VOD was found to be 2.15 times higher in mismatched family or unrelated allogeneic recipients as compared to HLA-identical sibling transplants. The use of methotrexate as prophylaxis of GVHD is associated with an increased risk of VOD as compared to the use of cyclosporine alone or together with corticosteroids.

Clinical aspects

Clinical history
Usually, an unexplained weight gain is the first symptom of VOD. This weight gain, attributable to water and sodium retention by the kidney, appears within 6 to 8 days following the transplant in 95% of patients that develop VOD. Two to three days later, hyperbilirubinemia of varying degrees is observed in 98% of the cases. An increase in aspartate aminotransferase and alkaline phosphatase may occur simultaneously or a few days later. Most patients develop ascites and pain in the upper right quadrant, and clinical examination usually reveals a firm and painful hepatomegaly. Many patients become refractory to platelet transfusions. Renal insufficiency is also present in 50% of patients developing VOD and 25% of them will require hemodialysis. Finally, patients with severe VOD can display severe encephalopathy or even become comatose.

Outcome
In 50 to 80% of the cases, a gradual improvement of the clinical condition is noted at 2 to 4 weeks after the onset of the disease. In the remaining 20 to 50% of the cases, patients die because of or with severe VOD. The majority of them die of multiple organ failure (MOF) with hepatic failure, but also of renal failure, congestive heart failure, extravascular fluid effusions, and pulmonary failure requiring oxygen support and mechanical ventilation. The reasons for lung failure may include pulmonary VOD, pleural effusions and interstitial pneumonitis of infectious or non-infectious origin. Bleeding at gastrointestinal sites or at other sites is a significant cause of death as well. The Seattle group has developed an elaborate regression model that estimates the probability of developing severe (mortal) VOD based on early measurements of serum bilirubin and the percent of weight gain. However, the sensitivity of these models is much lower than their specificity.

Diagnostic criteria

Clinical picture
Although theoretically the diagnosis of VOD should be based on the histological examination of the liver, the risk of bleeding during a liver biopsy in thrombopenic patients who are often refractory to platelet transfusions is such that the diagnosis is very often only a clinical one. The Seattle and Baltimore groups have set up similar diagnostic criteria for VOD (Table 1). Although the diagnostic accuracy of these protocols is excellent when all criteria are met, other groups have found that their sensitivity and specificity diminish in the early diagnosis of VOD when only 2 criteria are present. However, in this case, a liver biopsy is not very sensitive, partly because of the heterogeneity of VOD lesions throughout the liver. It is not yet clear whether the modification of the Seattle criteria (Table 1) will improve their sensitivity and specificity. Patients who meet modified Seattle criteria for VOD but have another cause of liver dysfunction (Table 3) or patients who meet only one of the modified Seattle criteria all have liver dysfunction of uncertain causes. In McDonald’s study of 355

<table>
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<th>Table 3. Differential diagnosis of VOD.</th>
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<td>1) After allogeneic BMT:</td>
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<td>1. Acute liver GVHD</td>
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<td>2. Cyclosporine-induced hepatotoxicity</td>
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<td>2) After autologous or allogeneic BMT:</td>
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<tr>
<td>1. Fungal infiltration of the liver</td>
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<td>2. Viral hepatitis</td>
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<td>3. Cholangitis lenta, e.g. during sepsis</td>
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<td>4. Drug (trimethoprim-sulfamethoxazole, some third-generation penicillins, fluconazole and itraconazole) induced liver dysfunction</td>
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<td>5. Constrictive pericarditis and right congestive heart failure</td>
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<td>6. Persistent tumor infiltration of the liver</td>
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and hepatocyte necrosis and lead to gallstones. Cyclosporine, in a dose-dependent fashion, may cause cholestasis also induce liver dysfunction.

The bilirubin level can exceed 10 mg/dL, but ascites, weight gain and fluid retention is usually sufficient to differentiate VOD from other causes of early liver dysfunction. Fungal infiltration of the liver usually causes tender hepatomegaly, fever, and markedly elevated serum alkaline phosphatase levels (which are unusual with VOD). However, fungi (mainly Candida species) can also invade blood vessels, causing hepatic infarctions or venous obstructions that produce tender hepatomegaly, ascites and signs of portal hypertension mimicking VOD. Viral infections of the liver are unusual in the early post-transplant period because of the systematic use of acyclovir and because B and C hepatitis viruses can produce liver injury only in the presence of an intact immune system. Cholangitis lenta follows sepsis and other causes of cytokine release. The bilirubin level can exceed 10 mg/dL, but ascites, weight gain and renal failure are unusual.

Medications used in the transplant setting can also induce liver dysfunction. Cyclosporine, in a dose-dependent fashion, may cause cholestasis and hepatocyte necrosis and lead to gallstones. Total parenteral nutrition, some antimicrobial drugs (such as trimethoprim-sulfamethoxazole, some third-generation penicillins, fluconazole and itraconazole) and methotrexate can produce both cholestasis as well as hepatocellular injury as well.

Constrictive pericarditis and right congestive heart failure can cause pain in the upper right quadrant, hepatomegaly, ascites, peripheral edema and pleural effusions, as well as renal failure and an increase in the concentration of serum hepatic enzymes. Both diseases can be ruled out by normal echocardiography.

Finally, in patients with refractory disease, persistent tumor infiltration of the liver should be considered.

### Differential diagnosis

Other liver diseases are common after BMT (Table 3). However, the presence of weight gain and fluid retention is usually sufficient to differentiate VOD from other causes of early liver dysfunction.

Acute liver GVHD causes jaundice with increased serum alkaline phosphatase levels and aminotransferase levels. Ascites, liver failure and encephalopathy are unusual. AGVHD usually develops between days 20 and 40 post-transplant together with skin and/or gut GVHD. However, the differential diagnosis with VOD can be difficult when GVHD develops earlier (hyperacute GVHD) or when the onset of VOD is later than day 10. Moreover, both diseases are common after allogeneic BMT and may thus coexist. In this case, measurement of the hepatic venous pressure and/or a histologic evaluation of the liver may be helpful in determining which disease is dominant.

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### Table 4. Reasons for assigning patients to the group of liver disease of «uncertain cause» in the McDonald’s study (ref. #9).

| Signs of VOD not meeting modified Seattle criteria: | 35% |
| Other liver disease within 20 days of bone marrow infusion: | |
| sepsis: 28% | |
| GVHD: 22% | |
| cardiac failure: 8% | |
| persisting tumor infiltration of the liver: 4% | |

Died before liver disease could become clinically apparent: 4%.

**Histology**

When the diagnosis cannot be made clinically (because the timing of symptoms is modified by therapies affecting the natural evolution of the disease, or only two out of the 3 Seattle criteria are present, or clinical data suggest another cause of hepatic disorder), and aggressive therapy is required, a transjugular liver biopsy can be carried out. This further allows for the measurement of the hepatic venous pressure gradients (HVPG), which favor VOD if greater than 10 mm Hg and shows a high prognostic value. However, because of the risk of bleeding which may be fatal or preclude beneficial therapy, and because of low sensitivity in patients not meeting clinical criteria, the role of transjugular liver biopsy is still debated. It should be noted that the risk of complications after measurement of HVPG alone (without liver biopsy) is low, and this may be useful in differentiating VOD from GVHD.

Another interesting approach is the laparoscopic liver biopsy. This technique was recently evaluated in a group of 29 patients, including 24 BMT recipients, with hepatic dysfunction after chemotherapy. Thirty-two biopsies were obtained and all were informative. Furthermore, no procedure-related complication was noted and no patient required re-explo-ration.

From the histologic standpoint (Figure 1), the most distinctive feature of VOD is a thickening of the subintimal zone of central and sublobular venules, producing concentric or eccentric luminal narrowing. In the early stages, the changes consist of a marked widening of the subendothelial zone by fragmented red cells within an edematous proliferation where fibrinogen can be identified by a special stain (Mallory’s stain, Lendrum’s MSB technique) or immunochemistry. Thrombosis does not occur and inflammatory cells are few or absent. These obliterator lesions are focally distributed and can be obscured by the background features of acute venous outflow obstruction; they show pronounced centrlobular congestion, sinusoidal dilatation and hepatocyte loss. Therefore,
these early lesions can be missing or inconspicuous on routine stains, and the changes can be difficult to distinguish from sinusoidal congestion. Connective tissue stains (trichrome techniques) may help their identification.

In later stages, the subintimal lesion becomes fibrotic and can acquire an ingrowth of small vascular channels. Change in chronic venous outflow obstruction dominates the histological picture: perivenular fibrosis, pericellular fibrosis and central-central fibrous bridges develop and cirrhosis may ultimately appear. These late changes are non-specific and can be seen in other types of chronic outflow obstruction and cirrhosis as well. Hepatocyte hyperplasia of varying degrees and peliosis hepatitis have occasionally been found to accompany VOD and are particularly prominent in azathioprine-treated renal transplant patients.42

Connective tissue usually consists of a cellular portion in an enveloping framework of non-cellular substances, either of fibrous (collagen, reticular and elastic fibers), amorphous or gel types. A detailed review of the biochemical principles for staining of these substances is beyond the scope of this article.43 Many techniques are available for the differential analysis of the connective tissues, the most frequently used being the Van Gieson and Masson trichrome techniques (Figures 1 and 2). Trichrome stains, which employ three dyes, allow for the selective demonstration of muscle, collagen fibers, fibrin and erythrocytes. Three methods selectively demonstrate fibrin: Gram-Wegert, Mallory’s phosphotungstic acid, hematoxylin and Masson’s trichrome modified after Lendrum. Demonstration of elastic fibers is best achieved by the following techniques: Verhoeff, orcein, Weigert’s resorcin fuchsin and aldehyde fuchsin. Reticular fibers are best demonstrated by techniques that use silver salts, such as Gordon and Sweet’s method or Gomori’s method.

Other investigations

Other than the clinical picture and the histology, ultrasound studies may help in diagnosis by showing ascites, hepatomegaly or thickening of the gall-bladder wall, which are, in any case, all non-specific or unreliable findings. Pulsed Doppler ultrasound may show a decreased or inverted portal blood flow but this is a relatively late finding in patients with established VOD.46 A prospective study from Seattle46 was not able to identify any sonographic feature strongly associated with VOD in the early phases of the disease, when a definitive diagnosis is most needed.

Several laboratory parameters have been studied as potential markers of VOD. Serum procollagen III47 or its N-terminal peptide 48 have been found to be early markers of VOD even before any clinical sign of the disease. Contrary to protein S and antithrombin III, low protein C levels can discriminate between patients with or without VOD, but this is a predictive test rather than a specific marker, because the difference between the two groups is already evident before conditioning.13 Finally, a recent study49 has shown that the level of plasminogen activator inhibitor 1 (PAI-1) was significantly elevated at the time of bilirubin increase in patients with VOD as compared with patients with GVHD or other causes of hepatic damage.

Prevention

Given the very high mortality rate in patients with severe VOD, it is critical to prepare effective preventive strategies during hematopoietic stem cell transplants. Preventive measures have essentially been based on four different molecules: heparin,
prostaglandin E1, pentoxifylline and ursodeoxycholic acid.

The usefulness of low-dose heparin has been shown in a prospective randomized study conducted by Attal,50 who compared a control group and a group receiving heparin at a dose of 100 U/kg/d from day –8 until day +30 after autologous and allogeneic BMT. The incidence of VOD decreased from 13.7% in the control group to 2.5% in the heparin group. However, there was no difference in the incidence of severe VOD which was very low in both arms. In a double-blind, placebo-controlled study in 61 patients undergoing autologous or allogeneic BMT, the low molecular weight heparin enoxaparin was shown to significantly reduce the incidence and duration of VOD, but severe VOD was not reported in the placebo group.51 In addition, platelet engraftment was accelerated, platelet transfusion was reduced, and hemorrhagic events were less frequent and less severe in the treated group. Thus, although the administration of low-dose heparin appears to be safe, it remains to be shown in a large randomized trial that severe VOD can be prevented in high-risk patients.

In 1989, Gluckman52 reported a study in which prostaglandin E1 (PGE1) was administered at a dose of 3 μg/kg/h from the start of the preparative regimen until day 30 post-transplant in leukemic patients undergoing allogeneic BMT. The incidence of VOD decreased from 39.1% in the historical control group to 12.8% in the treated group, most notably in patients with previous hepatitis. However, others53 were not able to reproduce these results in patients at high risk of VOD, and noted considerable toxicity precluding full completion of the treatment.

Pentoxifylline (PTX) is a methylxanthine analogue which can inhibit transcription of TNF-α. In a non-randomized study, the administration of PTX considerably reduced the incidence of VOD and other toxicities compared to historical controls.14 However, randomized prospective studies have failed to show any advantage of PTX in the prevention of VOD or other toxicities associated with BMT.34

Ursodeoxycholic acid, an artificial bile acid, protects hepatocytes from damage caused by cholestasis. Essell55 reported a low incidence of VOD in patients receiving ursodeoxycholic acid prophylactically (which was fairly well tolerated). More recently, a prospective study by the same group56 showed that patients randomized for ursodeoxycholic acid developed significantly less VOD than patients receiving the placebo.

Finally, when high-dose radiotherapy (>12 Gy) is applied or when VOD occurs prior to completion of TBI, liver shielding may be used to reduce hepatic toxicity, although its efficacy is not demonstrated and its effect on tumor eradication remains unknown.

**Treatment**

While more knowledge about the pathophysiology of VOD has allowed for the proposal of such prevention, it also lays the ground for therapeutic measures, including supportive care, PGE1, r-tPA, and liver transplantation.

Supportive care is aimed at maintaining intravascular volume and renal perfusion while avoiding extravascular fluid accumulation.11 This involves restriction of the sodium supply and diuretic therapy with loop diuretics or spironolactone. Perfusion of albumin concentrates or colloids can help maintain the intravascular volume, but will eventually accumulate in extravascular spaces. Therefore, preference should be given to the transfusion of red cells to maintain the hematocrit above 38-40%. Several groups have advocated continuous perfusion of dopamine to maintain renal blood flow, but its real value has not been proven. Finally, when fluid accumulation cannot be controlled, hemodialysis is necessary. When ascites limit breathing, paracentesis may be required. Encephalopathy should be treated with protein restriction and oral lactulose. The use of peritoneovenous shunts can improve symptomatology, but runs a very high risk of serious complications.

There are also approaches aimed at reversing venular occlusion. There are only brief reports of PGE1 improving established moderate VOD.11. Recombinant tissue plasminogen activator (r-tPA) has been used in several centers. The largest experience was reported by the Seattle57 group in 42 patients receiving 5 to 120 mg of r-tPA over 2-4 days together with low-dose heparin. Twelve (29%) patients responded, but with a substantial risk of serious bleeding. Non-responders included those requiring supplemental oxygen, mechanical ventilation or dialysis before the start of r-tPA.

Defibrotide, a novel polydeoxyribonucleotide, has several properties of potential interest for the treatment of VOD, such as the increase of endogenous tissue plasminogen activator and the decrease of plasminogen activator inhibitor type 1. Richardson et al.58 treated eight patients with severe VOD using defibrotide. Complete responses were achieved in three patients, none of whom had responded to r-tPA.

Several groups have used portosystemic shunting in order to decrease portal hypertension. Surgical shunting is possible,59 but because few patients with severe VOD are reasonable candidates for surgery, the most interesting technique appears to be transjugular intrahepatic portosystemic stent-shunt (TIPS).60-62 This technique consists in creating an intraparenchymal channel (kept permeable with a metal stent) between a main branch of the portal vein and a hepatic vein using a percutaneously inserted transjugular catheter. Although TIPS improved clinical status and liver function in a few
patients, more extensive experience should be accumulated on the risks and efficacy of the procedure. Finally, as a last resort in case of life-threatening hepatic failure, orthotopic liver transplantation can be considered. However, very few patients who have received a liver transplant for acute VOD have become long-term survivors.

Perspectives and conclusions

VOD is a serious complication of high-dose regimens used as conditioning before BMT, for which a number of risk factors have been identified. We favor the systematic use of low-dose heparin (100 U/kg/d) or low molecular weight heparin, starting with the conditioning regimen and continuing through day 21 post-transplant, in all patients undergoing autologous or allogeneic BMT. For patients particularly at risk for developing severe VOD, we add ursodeoxycholic acid during the same period. It is of utmost importance to identify signs of VOD as early as possible, so that supportive care can be adapted accordingly. The differential diagnosis with acute GVHD or liver infections is critical because these complications may coexist, particularly in allogeneic transplant recipients, and their management is radically different and not devoid of serious side effects. In this setting, a transjugular measurement of HVPG and even a liver biopsy may be needed when clinical diagnostic criteria such as those proposed by the Seattle and Baltimore groups are not met or when concomitant disorders are suspected. Aggressive therapeutic intervention, such as r-tPA 20-40 mg continuous infusion over 3-4 days, should be initiated early (in order to avoid multigran failure), but should be performed only in those patients who could benefit from this in the face of rapidly progressive VOD. Insertion of TIPS by an experienced hand may be a valid option in patients with major counter-indications or no response to r-tPA, whereas the role of defibrotide remains to be determined.

References