

* CHAPTER 11

Early complications after HSCT

1. Introduction

The high doses of RT and/or CT included in conditioning regimens (see Chapter 8) affect all organs and tissues of the recipient, producing several early and late secondary effects of variable intensity. The most common early effects such as nausea, vomiting, mucositis and pain are discussed in Chapter 10, and late effects are covered in Chapter 15. Here we summarise some other early complications that, albeit infrequent, are an important cause of morbidity and mortality.

2. Haemorrhagic cystitis

Haemorrhagic cystitis (HC) can be a serious complication of HSCT and causes significant morbidity, prolongation of hospitalisation, and, occasionally, death. Various additional complications have been described in patients with HC: obstructive uropathy, hydronephrosis, tubulointerstitial nephritis, acute renal failure and bladder perforation.

2.1. Clinical features

Haematuria, symptomatic or asymptomatic, is graded as follows: grade I, microscopic; grade II, macroscopic; grade III, with clots; and grade IV, requiring instrumentation for clot evacuation or leading to urinary retention or requiring surgical intervention (1).

2.2 Pathogenesis

Early bleeding (up to 72 hrs after CT agents) occurs almost exclusively when using conditioning therapies including Cy, whose metabolite acrolein produces direct toxicity to the urothelium. The risk of developing HC after Cy is dose dependent. Occasionally, other agents such as ifosfamide, Bu (especially if associated with Cy), VP16 or TBI have been implicated.

Episodes of HC occurring late (usually more than 2 weeks after HSCT) are classically attributed to BK polyomavirus infection (and exceptionally to infections with other polyomaviruses, adenovirus or CMV). However, the role of BK viraemia and viruria on the development of HC is not clear, as many patients with BK infection do not develop HC. This fact, and the higher incidence of late-onset HC in allo-HSCT from alternative donors and in patients with advanced age, GvHD and thrombocytopenia, suggests that the pathogenesis of HC may be multifactorial. Several - but not all - authors have observed a similar incidence of late-onset HC in patients receiving RIC and in those undergoing MAC-HSCT (1, 2).

2.3 Incidence

HC secondary to Cy is seen in 5–25% of cases, depending on the preventive

measures adopted. Late HC was reported in a recent series as occurring in 7% of patients with RIC vs 17% of those undergoing MAC-HSCT and up to 58% in patients receiving MAC-HSCT from haplo or cord blood HSCT who had positive BK viruria (2).

2.4 Prophylaxis

Continuous irrigation of the bladder has been abandoned because it produces more haematuria and urinary tract infections than does Mesna. Although most centres use Mesna as a prophylaxis for Cy-based regimens, several randomised studies have shown that this drug does not offer additional benefits if hydration and diuresis are adequate. The recommended daily dose for hydration is 3 L/m². If used, the daily dose of Mesna should be 1.0–1.5 × the daily dose of Cy, administered iv using one of the following schedules:

- a. As a continuous infusion in 1 L of 0.9% saline over 12–24 hrs, beginning 4 h prior to the 1st dose of Cy;
- b. As bolus injections of 20% of the daily dose of Cy administered as a bolus ½–1 hr before Cy and the remaining daily dose divided into bolus injections q 2–3 hrs;
- c. By combining continuous infusion with intermittent bolus injections.

Whichever regimen is used, the presence of acrolein in the bladder 24 hrs after Cy makes it advisable to prolong mesna administration for 24 hrs after the last Cy dose.

2.5 Treatment

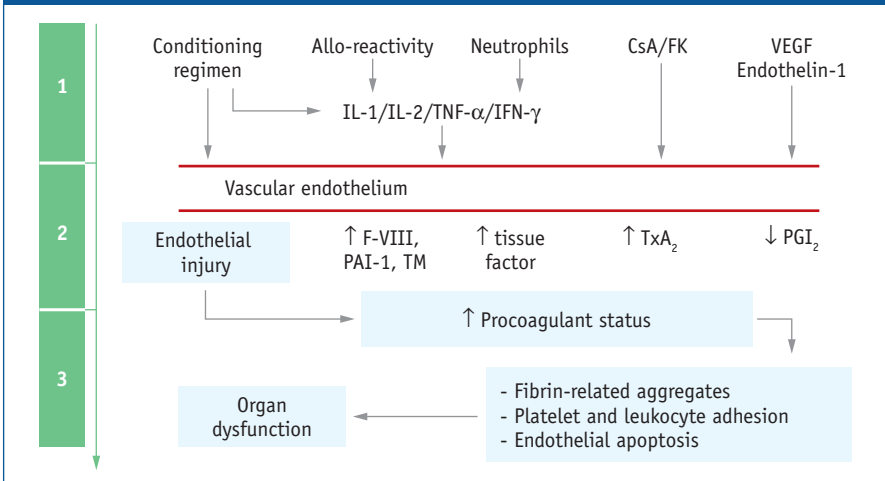
Treatment should be based on a three-step approach as follows:

- a. Forced hydration plus intensive platelet support. The use of procoagulant agents such as aminocaproic acid is contraindicated as they favour clot formation in the bladder.
- b. Continuous bladder irrigation (via transurethral or suprapubic cystotomy) with saline. Some success has been reported with bladder instillation of formalin, alum, silver nitrate, sodium hyaluronate, prostaglandin E2, GM-CSF or fibrin glue as well as with the administration of palifermin, hyperbaric oxygen, oestrogens, or recombinant FVIIa. Similarly, systemic or intravesical cidofovir, ciprofloxacin (reduces BK replication) or ribavirin have been reported as effective for cases of HC attributable to BK or adenovirus.
- c. If the above measures do not alleviate HC, other salvage approaches can be considered: selective embolisation of bladder arteries (one of the simplest and most effective measures in the hands of an expert angioradiologist); catheterisation of both ureters to rest the bladder; hypogastric bond (which can produce sexual impotence) or, as a last resort, cystectomy.

3. Early complications of endothelial origin

There are a number of complications where injury to the vascular endothelium seems to be the most important initial event. These have imprecise diagnostic criteria and overlapping clinical features and are observed within the first 30–60 days after HSCT. The best-defined syndromes resulting from this endothelial injury are: 1. veno-occlusive disease of the liver; 2. capillary leakage syndrome; 3. engraftment syndrome; 4. diffuse alveolar haemorrhage; and 5. HSCT-associated thrombotic microangiopathy (3). This endothelial injury seems also to have a relevant role in the pathogenesis of GvHD (see Chapter 13). Figure 1 shows their common pathogenesis.

Figure 1: Common pathogenesis of early complication of vascular origin after HSCT



VEGF: vascular endothelial growth factor; Tx: thromboxane; PG: prostaglandin; TM: thrombomodulin; PAI-1: plasminogen activator inhibitor type 1

3.1 Hepatic veno-occlusive disease

3.1.1 Definition

Hepatic veno-occlusive disease (VOD) is the term used to designate the symptoms and signs that appear early after HSCT as a consequence of conditioning regimen-related hepatic toxicity. This syndrome is characterised by jaundice, fluid retention and tender hepatomegaly appearing in the first 35–40 days after HSCT (4–7).

3.1.2 Pathogenesis

The hepatic metabolism of certain drugs (e.g. Cy) by the cytochrome P450 enzymatic system produces several toxic metabolites (e.g. acrolein). These toxic metabolites are converted into stable (non-toxic) metabolites by the glutathione (GSH) enzymatic system and eliminated. When this process occurs in patients with a reduced GSH activity caused by previous liver disease or by the action of agents such as Bu, BCNU or TBI, which consume GSH, toxic metabolites are not metabolised. Toxic metabolites are predominantly located in area 3 of the hepatic acinus (around the centrilobular veins) because this area is rich in P450 and poor in glutathione. Consequently, damage to hepatocytes and sinusoidal endothelium occurs predominantly in this zone. The remaining factors listed in Figure 1 can also contribute to endothelial injury.

Experimental models show that the first events after endothelial injury caused by toxic metabolites are loss of *fenestrae* in sinusoidal endothelial cells (SEC), formation of gaps within and between SEC and rounding up or swelling of SEC. Consequently, red blood cells penetrate into the space of Disse and dissect off the sinusoidal lining cells, which embolise downstream and block the sinusoids, reducing the hepatic venous outflow and producing post-sinusoidal hypertension. Based on all these observations, some authors have proposed the term of sinusoidal obstruction syndrome for this complication (8).

3.1.3 Clinical features

Classical VOD. Several days after conditioning (from days -1 to +21) there is the presence of jaundice (in almost 100% of cases), hepatomegaly and/or right upper quadrant pain and weight gain (not attributable to an excessive fluid administration) together with oedema and ascites (4).

Late VOD. This shows the same clinical manifestations as classical VOD but develops late after HSCT (one-third of cases occur after patient discharge). It is mainly observed after conditioning including the use of one of several alkylating agents (e.g. busulfan, melphalan or thiotepa). One-third of cases show a biphasic course with an initial and transitory peak followed by a definitive late phase (9).

VOD with multi-organ failure. This shows the previously described clinical manifestations plus thrombocytopenia (refractoriness to platelet transfusions); pleural effusion, pulmonary infiltrates, progressive renal, cardiac and pulmonary failure, confusion, encephalopathy, and coma (6, 7).

3.1.4 Incidence

This has ranged from 3% to 54% in the largest series. This variability is a

consequence of the presence or absence of the well-known risk factors for this complication (see below). In the only prospective multi-centre study published, the incidence of VOD was 8% in cases of allo-HSCT and 3% in cases of auto-HSCT (5). In a large single-centre study, the cumulative incidences of VOD in cases of allo-HSCT in the last decade were 14% and 8% using Seattle or Baltimore criteria, respectively. The incidence in patients undergoing RIC-HSCT seems to be less than 2% (7).

3.1.5 Risk factors

See Table 1 (4, 6, 7, 9).

Table 1: Risk factors for VOD

Risk	Lower risk < Higher risk
Transplant type	Syngeneic or autologous < allogeneic
Donor type	Sibling < another relative < unrelated
HLA compatibility	HLA match < any mismatch
Stem cell origin	Peripheral blood < bone marrow
T-cell depletion	With TCD < without TCD
Diagnosis	Non-malignant disease < malignant disease
Status of the disease	Remission < relapse
Conditioning	
- Intensity	Cy alone < Cy + TBI < BVC ^(a)
- TBI	Fractionated TBI < single dose TBI
	Less than 12 Gy < more than 12 Gy
	Low dose rate < high dose rate
- Busulfan	iv Bu < adjusted oral Bu < non adjusted oral Bu
- Timing	Interval Cy – TBI 36 hours < 12 hours
Age/Sex	Younger < older/men < women
Karnofsky index	100–90 < lower than 90
ASAT/ALAT before HSCT	Normal < high
Transplant number	First < second
Previous hepatic irradiation	No < yes
Previous Mylotarg	No < yes ^(b)
Status of the liver	Normal < fibrosis < cirrhosis or infiltration
CMV serological status	Negative < positive
Fever in conditioning	Absent < present
Hepatotoxic drugs	Progestogens, ketoconazole, CsA, methotrexate, amphotericin B, vancomycin, acyclovir, iv Ig ^(c)
Genetic predisposition	GSTM1 positive < GSTM1 null genotype ^(d)

The most important risk factors are indicated in bold type. (a) BVC (BCNU, VP, Cy). (b) VOD incidence up to 64% (Wadleigh et al. *Blood* 2003). (c) Higher incidence of VOD with high-dose iv Ig (Cordonier et al. *Ann Intern Med* 2003). (d) Srivastava et al. *Blood* 2004

3.1.6 Diagnosis

As for any syndrome, the diagnosis of VOD must be established clinically. All teams employing HSCT use one of the following two sets of clinical criteria (4, 6, 7).

Seattle criteria. In the first 20 days after HSCT, the presence of two or more of the following: bilirubin >2 mg/dL (>34 mmol/L); hepatomegaly or pain in the right upper quadrant; weight gain ($>2\%$ basal weight).

Baltimore criteria. In the first 21 days after HSCT, the presence of bilirubin at >2 mg/dL (>34 mmol/L) plus two or more of the following: painful hepatomegaly, ascites or weight gain ($>5\%$ basal weight).

In both diagnostic criteria, other possible causes of these clinical features should be excluded before accepting a diagnosis of VOD (see differential diagnosis). Additionally, it is necessary to remember that some cases of VOD can appear late after HSCT. Other studies that can complement the diagnosis are as follows.

Haemodynamic studies of the liver. These are carried out through the jugular or femoral veins (10). Despite its usefulness, this procedure is only indicated to confirm the diagnosis of VOD if it is required to decide on a therapeutic approach, as it can be potentially hazardous for the patient. An hepatic venous gradient pressure (HVGP) of ≥ 10 mmHg in a patient without a previous liver disease allows a precise differential diagnosis with a high degree of specificity. However, a normal HVGP does not exclude this syndromic diagnosis.

Liver biopsy. The thrombocytopenia usually present in this phase after HSCT precludes a transperitoneal liver biopsy. Consequently, hepatic tissue can only be obtained by means of a transvenous biopsy in the course of a haemodynamic study. In addition to the classical histological changes seen with VOD (concentric non-thrombotic narrowing of the lumen of small intrahepatic veins), other less specific abnormalities can be observed (e.g. eccentric narrowing of the venular lumen; phlebosclerosis; sinusoidal fibrosis or hepatocyte necrosis). Because of the patchy nature of VOD, a normal biopsy does not exclude this syndromic diagnosis.

Ultrasonography. A variety of abnormalities can be observed, such as gallbladder wall thickening, ascites, hepatomegaly and attenuated or reversed portal flow, but they are all non-specific.

Biological studies. Although the serum of patients with VOD shows an increase in levels of plasminogen activator inhibitor (PAI)-1 (marker with the highest specificity and sensitivity for VOD), vWF, thrombomodulin, E-selectin, sICAM, aminopropeptides of type III collagen and hyaluronic acid, they are all of little utility in daily clinical practice (4).

3.1.7 Differential diagnosis

To accept a diagnosis of VOD, all of the following possible causes of similar clinical

features should be excluded as far as possible.

Infections. These include *Cholangitis lenta* (sepsis of the liver), fungal infections and viral hepatitis.

Immune dysfunction. This can lead to hepatic GvHD or autoimmune hepatitis.

Drug toxicity. This can arise from CsA, azoles, MTX, progestogens, trimethoprim-sulfamethoxazole and TPN, among others.

Reduction of venous outflow. This can lead to increased volume, constrictive pericarditis, congestive heart failure, fluid overload or renal failure.

Other causes. These include pancreatic ascites, chylous ascites or infiltration of the liver.

3.1.8 VOD prophylaxis

See Table 2 (4, 11).

Table 2: VOD prophylaxis

To avoid risk factors

- When possible, delay HSCT if an acute hepatitis exists; adjust Bu dose or use iv Bu; use first Cy than Bu; fractionate TBI; avoid hepatotoxic drugs, etc.
- In high risk patients, consider RIC allo-HSCT (incidence of VOD <2%) (7)

Pharmacological

- Sodium heparin: 100 U/kg/day by continuous infusion. Despite two randomised studies showing a beneficial effect others have suggested that it is ineffective and dangerous.
- Prostaglandin E1: 0.3 µg/kg/h by continuous infusion. Evaluated in several clinical trials usually combined with heparin. When administered alone no beneficial effect was observed.
- Ursodeoxycholic acid: 600–900 mg/day *per os*. Four randomised trials and 2 historically controlled studies have shown a reduction in VOD and TRM.
- Low molecular weight heparin: enoxaparin 40 mg/day or fraxiparin 5000 U/day s.c. Relatively safe, may have some effect; a randomised study is needed.
- Defibrotide. Only one randomised study in children showing a clear reduction in the incidence of VOD and GvHD (11).

3.1.9 VOD treatment

See Table 3 (4, 6, 12).

3.1.10 VOD evolution

See Table 4 (4, 6, 7, 12).

3.2 Capillary leak syndrome (CLS)

3.2.1 Pathogenesis

Injury to the capillary endothelium (probably caused by cytokines and VEGF)

Table 3: VOD treatment

First line therapy	
Symptomatic ^(a)	<ul style="list-style-type: none"> • Restriction of salt and water intake ± diuretics • Maintain intravascular volume and renal perfusion by means of albumin, plasma expanders and transfusions (haematocrit >30%)
Specific	<ul style="list-style-type: none"> • DF: 6.25 mg/kg iv in 2 h infusion q 6 h x 14 d → 50-55% CR in severe VOD with MOF and 47-60% of survival at day +100 with no secondary effects (15) • Other agents ^(b, c)
Other measures	
Symptomatic ^(a)	<ul style="list-style-type: none"> • Analgesia • Paracentesis/thoracocentesis • Haemodialysis/haemofiltration • Mechanical ventilation
Specific	<ul style="list-style-type: none"> • TIPS (transvenous intrahepatic portosystemic shunt) ^(d) • Surgical shunt • Liver transplantation

DF: defibrotide; MOF: multiorgan failure. (a) Symptomatic treatment should be established first, reserving specific measures for most severe cases. (b) rt-PA (recombinant tissue plasminogen activator) (0.05 mg/kg/h in 4 h (max. 10 mg/d) during 2-4 d) usually combined with sodium heparin (20 U/kg as a bolus (max. 1000 U) followed by 150 U/kg/day by continuous infusion for 10 days) was frequently used before defibrotide became available. Although rt-PA is effective in some cases, its use is contraindicated in patients with multiorgan failure, haemorrhage or severe hypertension. (c) Occasional successes have been reported with antithrombin III, prostaglandin, corticosteroids, glutamine/vitamin E, N-acetylcysteine, and human recombinant soluble thrombomodulin but the reported series are small precluding any recommendation. (d) Although portal hypertension and ascites improve, long term efficacy and survival are extremely poor.

produces a loss of intravascular fluids to the interstitial space, which leads to the clinical manifestations of CLS (13).

3.2.2 Incidence

The absence of well-established clinical criteria for the diagnosis of CLS precludes an adequate estimation of its incidence. Additionally, the differential diagnosis from VOD, engraftment syndrome (ES) or DAH can be very difficult.

3.2.3 Clinical features

This is characterised by the development in the first 15 days after HSCT of weight

Table 4: VOD evolution

	Classification ^(a)	Frequency ^(b)
CR at day +100 without treatment	Mild VOD	8–23%
CR at day +100 with treatment	Moderate VOD	48–64%
Non-CR before death ^(c) or day +100	Severe VOD	23–28%
Mortality attributable to VOD by day +100 in classical series ⁽⁴⁾ ^(d)	1–3% of all HSCT 18–28% of all VOD 75–95% of severe VOD	
Cumulative incidence of dying from VOD by day +100 in HSCT performed since 1997 ⁽⁷⁾ ^(e)	2% of all HSCT 14% of all VOD 50% of severe VOD	
Mortality of severe VOD with MOF ⁽⁷⁾	without DF: 78%	with DF: 25%

CR: complete remission; DF: defibrotide; MOF: multi-organ failure; (a) Classification described by Seattle group to evaluate VOD retrospectively. (b) Values observed in the two largest series. (c) In many cases VOD is not the direct cause of death but contributes to it. (d) Data from pre-defibrotide era. (e) Using Baltimore clinical criteria

gain (>3% within 24 hrs) and generalised oedematous syndromes (e.g. ascites, pleural effusion or pericarditis) that characteristically do not respond to furosemide treatment. Other features occasionally observed are tachycardia, hypotension, renal insufficiency of pre-renal origin and hypoalbuminaemia (13, 14).

3.2.4 Differential diagnosis

From ES: its earlier development, the absence of skin rash and the poor response to corticosteroids. From VOD: the absence of jaundice and painful hepatomegaly and the poor response to furosemide. From DAH: generalised oedema.

3.2.5 Risk factors

The use of G-CSG, GM-CSF or K-CSF; high cumulative doses of CT in the pre-HSCT phase; unrelated or HLA-mismatched donor grafts.

3.2.6 Treatment

Withdraw any growth factors. Despite being used systematically, corticosteroids offer poor responses. iv Ig and bevacizumab (anti-VEGF) have been used successfully in some cases (14).

3.2.7 Evolution

There is a high mortality rate if CLS progresses to multi-organ failure.

3.3 Engraftment syndrome

This syndrome has received other names in the literature: capillary leak syndrome at engraftment; auto-aggression syndrome; peri-engraftment respiratory distress syndrome (PERDS); and aseptic shock syndrome (15-17).

3.3.1 Pathogenesis

This involves a massive release of pro-inflammatory cytokines (e.g. IL-2, TNF- α , IFN- γ and IL-6), M-CSF, EPO, products of degranulation and oxidative metabolism of neutrophils and systemic endothelial damage.

3.3.2 Incidence

ES is almost exclusively diagnosed after auto-HSCT. In this setting, the incidence ranges from 5% to 25% (13% in the largest series). It is rarely seen after conventional allo-HSCT, but is occasionally described after RIC allo-HSCT and CB-HSCT (18).

3.3.3 Clinical features and diagnostic criteria

The clinical manifestations and the Spitzer and Maiolino diagnostic criteria are listed in Table 5 (13, 16). A recent study showed that the Maiolino criteria - when correctly applied - are the best tool to establish an early diagnosis, despite being less specific than the Spitzer criteria. A sudden and significant increase in the level of C-reactive protein can help to establish the diagnosis (17).

Table 5: Clinical criteria for diagnosis of ES

Major clinical criteria	Minor clinical criteria
Non-infectious fever ¹ Skin rash ² Pulmonary oedema ³ , hypoxaemia	Weight gain ⁴ Hepatic or renal dysfunction ⁵ Transient encephalopathy ⁶
Spitzer criteria (15)	Maiolino criteria (16)
3 major criteria, or 2 major and 1 minor criteria, within 96 h of engraftment	Non-infectious fever ¹ + skin rash, or pulmonary infiltrates, or diarrhoea ⁷ , from 24 h before or at any time after the first appearance of neutrophils ⁸

¹New fever (>38°C) without clinical or microbiological documentation or response to antimicrobial treatment. ²Maculo-papular exanthema involving >25% body surface area. ³Documented by X-ray or CT without signs of infection, cardiac failure or pulmonary embolism. ⁴Higher than 2.5% of basal. ⁵Bilirubin ≥ 2 mg/dL (34 μ mol/L) or ASAT/ALAT ≥ 2 times or creatinine ≥ 2 times normal. ⁶If unexplainable by other causes. ⁷At least two episodes of liquid stools/day without microbiological documentation of infection. ⁸The original sentence "24 h before or after" is confusing and has generated incorrect interpretations in some papers

3.3.4 Risk factors

Most cases of ES were described following the introduction of growth factors and PBSCT. Nowadays, ES is mainly observed in patients who have not received intensive chemotherapy before undergoing auto-HSCT or in those receiving less intensive conditioning, as occurs in cases of breast cancer, amyloidosis, myeloma, POEMS or autoimmune diseases (17).

3.3.5. Treatment

Methyl-PDN 1 mg/kg q 12 hrs (for 3 days) with progressive tapering off over 1 week. Because of the difficulty of excluding an infectious origin of the fever, this treatment should not be started until it has been confirmed that the fever does not respond to empirical antibiotic therapy and that cultures are negative.

3.3.6 Evolution

There is complete resolution in 1–5 days in >80% of the cases if steroids are introduced early. In some cases the symptoms reappear after stopping steroid therapy.

3.4 Diffuse alveolar haemorrhage (DAH)

The systematic use of bronchoscopy and bronchoalveolar lavage (BAL) to study these patients has permitted the recognition of DAH as a major entity after HSCT and allowed it to be differentiated from idiopathic pneumonia syndrome (IPS) (19, 20).

3.4.1 Pathogenesis

DAH seems to originate from the disruption of the alveolar–capillary basement membrane by conditioning, immune-mediated events and the return of neutrophils with marrow recovery. The pathological observations on small arteries are very similar to those observed in veins affected by VOD (20).

3.4.2 Incidence

The reported incidence ranges from 1% to 21% in cases of auto-HSCT and from 2% to 17% in cases of allo-HSCT.

3.4.3 Clinical features

The median times to onset in patients undergoing allo- and auto-HSCT are 19 and 12 days, but episodes after the first month are not uncommon. The main manifestations are as follows:

- Shortness of breath and non-productive coughing with or without fever; haemoptysis is rare.

- Hypoxaemia that can require oxygen therapy.
- Chest X-ray or CT findings with focal or diffuse interstitial or alveolar infiltrates located in the middle and inferior lung fields.

3.4.4 Diagnosis

This is based on BAL findings becoming progressively bloodier but not attributable to infection (absence of pathogens in BAL), on thrombocytopenia, fluid overload or heart failure. Successive aliquots of 20 mL, in at least three segmentary bronchi, become progressively more blood stained (indicating blood in the alveoli). The presence of hemosiderin-laden macrophages is usual but their mere presence is insufficient to diagnose DAH and their absence does not exclude the diagnosis as they can take 72 hrs to appear in the BAL.

3.4.5 Differential diagnosis

The differential diagnosis from IPS is very difficult. IPS usually appears after engraftment, predominantly in patients undergoing allo-HSCT. It does not respond to corticosteroids and progresses to fibrosis and respiratory failure in 85% of cases (only 15% in those with DAH). The differential diagnosis from PERDS (a form of ES) is almost impossible clinically but 2/3 of patients with PERDS do not show a progressively bloodier BAL.

3.4.6 Risk factors

DAH is not related to low platelet counts. Factors that favour this complication are older age, previous thoracic radiation, TBI and myeloablative conditioning.

3.4.7 Treatment

After some small retrospective series, high-dose methyl-PDN (250–500 mg q 6 hrs, 4–5 days and tapering over 2–4 weeks) was considered the treatment of choice. However, many other authors have failed to observe any benefit of corticosteroids on the poor outcome associated with DAH (19). No other measures have proved to be effective.

3.4.8 Evolution

The overall mortality rate ranges from 60% to 100% (80–100% if patients require mechanical ventilation). With steroid therapy, many patients do not develop respiratory failure (85%) but most of them die from multi-organ dysfunction syndrome or sepsis. Recent reports using non-invasive ventilation, lung-protective strategies and early diagnosis and treatment show that at the present the mortality

rate is around 50%. The prognosis is clearly better in patients with DAH appearing early after HSCT and in those receiving auto-HSCT (>70% of survivors) than those observed later or in an allo-HSCT setting (<25%) (19).

3.5 HSCT-associated thrombotic microangiopathy (TMA)

3.5.1 Pathogenesis

Conditioning regimens and other less well-known triggering factors produce a generalised endothelial dysfunction causing microangiopathic haemolytic anaemia and platelet consumption, resulting in thrombosis and fibrin deposition in the microcirculation. Unlike that seen in patients with classical TTP, ADAMTS13 activity in patients with TMA rarely decreases to below 10% of normal (21, 22).

3.5.2 Incidence

This is less than 4% in cases of auto-HSCT but up to 15% in cases of allo-HSCT (7% in an EBMT survey). There is a similar incidence after RIC and MAC-HSCT (22).

3.5.3 Clinical features

TMA usually develops around day +60, but early (day +4) and late (2 years) episodes have been described. It is characterised as follows.

- Microangiopathic haemolytic anaemia (MHA), defined as anaemia with >2–4% schistocytes, together with raised LDH and other markers of haemolysis.
- Thrombocytopenia or increased requirement for platelet transfusions.
- Renal dysfunction and/or neurological abnormalities such as cortical blindness, seizures and typical images in CT scans of the CNS.

In addition to these classical findings, experts insist on the relevance and high frequency of elevated blood pressure, diarrhoea secondary to intestinal TMA and proteinuria, as well as in the possible absence of renal and neurological symptoms (22).

3.5.4 Diagnosis

Table 6 shows the most used frequently clinical criteria, including a recently described category of “possible” TMA (23–25).

3.5.5 Risk factors

A higher incidence has been observed in patients receiving TBI, calcineurin inhibitors (CNI), sirolimus, unrelated or HLA-mismatched donor grafts, or developing GvHD or aspergillus, CMV or adenovirus infections. The intensity of conditioning does not seem to play a role in the development of TMA.

Table 6: Diagnostic criteria for HSCT-associated TMA

Blood & Marrow Transplant Clinical Trials Network consensus (23)

- 1) RBC fragmentation and 2 schistocytes per high-power field on PB smear
- 2) Concurrent increased serum LDH
- 3) Concurrent renal ^(a) and/or neurologic dysfunction w/o other explanations
- 4) Negative direct and indirect Coombs test

International Working Group of the EBMT (24)

- 1) Increased percentage (>4%) of schistocytes in peripheral blood
- 2) Thrombocytopenia <50 x 10⁹/L or a ≥50% decrease in platelet count
- 3) Sudden and persistent increase in LDH
- 4) Decrease in Hb concentration or increase in RBC transfusion requirement
- 5) Decrease in serum haptoglobin concentration

Probable TMA (25)

- 1) Increased percentage (>4%) of schistocytes in peripheral blood
- 2) Concurrent increased serum LDH
- 3) Thrombocytopenia <50 x 10⁹/L or a ≥50% decrease in platelet count
- 4) Negative direct and indirect Coombs test
- 5) Decrease in serum haptoglobin concentration
- 6) Absence of coagulopathy

(a) Doubling of serum creatinine or 50% decrease in creatinine clearance from baseline pre-HSCT

3.5.6 Clinical forms

Two main forms of TMA can be observed, as follows.

CNI-associated TMA is defined as MHA with or without (probable TMA) nephrotoxicity (or neurotoxicity). Classically, TMA develops early after HSCT. It is associated with the use of CNI and is usually reversible after stopping their administration. The relevance of recognising cases of probable TMA is that patients have an excellent prognosis.

TMA not associated with CNI toxicity presents with two clinical forms: a. TMA mimicking a haemolytic uraemic syndrome, primarily affecting the kidney and often causing oliguric or anuric renal failure with hypertension, MHA and thrombocytopenia; and b. fulminating multifactorial TMA, i.e. early after HSCT, characterised by renal failure, CNS disturbances, hypertension, MHA and thrombocytopenia, and associated with GvHD, viral or fungal infections. Most cases have a fatal evolution because the patients do not respond to treatment.

3.5.7 Prevention

The only reasonable measure is to keep close observation (2–3 times per week) of

the CNI, LDH and creatinine levels. If any of these markers increase, peripheral blood smears, haptoglobin levels and Coombs tests (direct and indirect antiglobulin tests) should be evaluated.

3.5.8 Treatment

The most effective measure is to stop CNI immediately (no dose reduction) by changing GvHD prophylaxis/treatment to another drug (corticosteroids, mycophenolate). Plasma exchange usually offers a poor response (median 35%; range 20–80%) probably because TMA is not associated with an absence or severe reduction of plasma ADAMTS13 activity and has a high associated mortality (80%). Some authors have reported successful results with defibrotide, rituximab, daclizumab and basiliximab therapies.

4. Idiopathic pneumonia syndrome (IPS)

4.1 Pathogenesis

IPS is the consequence of non-infectious lung injury after HSCT caused by the toxic effects of conditioning, immunological cell-mediated injury, inflammatory cytokines, flora-derived LPS and - probably - occult pulmonary infections (26, 27).

4.2 Incidence

Thanks to improvements in diagnostic methods, the incidence of IPS has fallen from more than 20% in earlier series of allo-HSCT to less than 10% at the present (around 8% and 2% after conventional and allo-RIC, respectively) (26). It is uncommon in the setting of auto-HSCT. Similarly, the median time of onset after allo-HSCT has moved from day +40–50 to day +18–21.

4.3 Clinical features

IPS is characterised by the development around day +20 of fever and non-productive cough, tachypnoea and hypoxaemia, and diffuse alveolar or interstitial infiltrates on X-rays or CT scans.

4.4 Diagnosis

Today, this diagnosis is accepted when there is evidence of:

- Widespread alveolar injury (clinical, radiological and/or functional); and
- Absence of active lower respiratory tract infection (all cultures and tests in BAL or lung biopsies are negative); and
- Absence of cardiac dysfunction, acute renal failure or iatrogenic fluid overload.

4.5 Clinical spectrum of IPS

Sometimes, additional studies allow the distinction of other entities among patients fulfilling IPS criteria. Categorised by the presumed site of the primary lung injury, the following are routinely included under the classification of IPS (26).

- a. Pulmonary parenchyma: acute interstitial pneumonitis, acute respiratory distress syndrome or delayed pulmonary toxicity syndrome.
- b. Airway endothelium: bronchiolitis obliterans syndrome or cryptogenic organising pneumonia (formerly bronchiolitis obliterans organising pneumonia) (see Chapter 15).
- c. Vascular endothelium: PERDS (a form of ES), CLS, or DAH.

4.6 Risk factors

These include the intensity of conditioning, use of TBI, allo-HSCT, older recipient age, acute leukaemia or MDS and the presence of GvHD.

4.7 Treatment

Supportive care measures (including non-invasive and invasive mechanical ventilation and haemofiltration), broad-spectrum antimicrobial agents and corticosteroids. Low or high doses of methyl-PDN seem to have limited efficacy (except in DAH forms of IPS). Preclinical and translational studies indicate that neutralisation of TNF- α might be a useful strategy. Etanercept given s.c. at the dose of 0.4 mg/kg twice weekly for a maximum of eight doses in combination with systemic corticosteroids seems to be well tolerated and efficacious in two-thirds of patients and to improve survival (28).

4.8 Evolution

Up to 60–80% of patients with IPS (95% if requiring mechanical ventilation) will die from progressive impairment of respiratory function.

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Multiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/online-training/handbook/>

1. Late onset haemorrhagic cystitis usually is produced by:

- a) The direct action of cyclophosphamide on the bladder.
- b) A polyomavirus infection
- c) A bacterial infection of the urinary tract
- d) The neutropenia

2. Which of the following complications could *not* be attributed to an endothelial dysfunction?

- a) Engraftment syndrome
- b) Veno-occlusive disease of the liver
- c) Haemorrhagic cystitis
- d) Thrombotic microangiopathy
-

3. Which of the following is not a clinical manifestation of VOD?

- a) Weight gain
- b) Ascites
- c) Platelet refractoriness
- d) Diarrhoea
-

4. All but one of the following are classical manifestations of engraftment syndrome

- a) Skin rash
- b) Back pain
- c) Fever
- d) Hypoxaemia
-

5. Which is the main cause of thrombotic microangiopathy after HSCT?

- a) Bacterial infection
- b) Graft allo-reaction
- c) Cyclosporin toxicity
- d) Renal failure