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REVIEWS

Liver Graft *versus* Host Disease after Allogeneic Peripheral Stem Cell Transplantation: Update on Etiopathogenesis and Diagnosis

R.-G. MIHĂILĂ[1]
[1]Faculty of Medicine, "Lucian Blaga" University of Sibiu, Sibiu 550169, Romania

Graft *versus* host disease (GVHD) is the main complication of allogeneic hematopoietic cell transplantation and is more frequent after peripheral stem cell transplants. Graft *versus* leukemia or lymphoma component of them is beneficial to eradicate residual tumor mass after previous treatment and conditioning regimen. A severe GVHD may endanger the patient's life. The most important liver manifestations of GVHD are increased serum alkaline phosphatase and bilirubin values. The last allows to estimate the GVHD severity. Sometimes, an increase of aminotransferases can mimic an acute hepatitis. Donor-derived hematopoietic cells appeared to turn in mesenchymal liver cells. Activated CD4(+) T cells, humoral and complement activation, a large number of cytokines and cytokine receptors are involved in GVHD development. Correct and early recognition of GVHD and its differentiation from the other liver diseases are essential for the medical practice.

Key words: allogeneic peripheral stem cell transplantation; apoptosis; graft *versus* host disease; liver; mesenchymal stem cells; tumor necrosis factor.

INTRODUCTION

Many complications of allogeneic peripheral stem cell transplantation have diminished as frequency and severity in the past years. The reduction of the intensity of conditioning regimens, the improvement of GVHD prevention strategies, and the disponibility of better supportive care are important scientific and practical achievements that contributed to this positive evolution. Some of the main challenges for today's and tomorrow's hematologists are human leukocyte antigen-mismatched and unrelated donor transplants, age-limit and expanding transplant indications [1].

Acute GVHD regularly involves skin, liver, gut, and lungs [2], while chronic GVHD is more frequently present at the skin, liver, mouth, and eyes [3]. After the skin, the second most frequent organ affected by GVHD is the liver. Its characteristic picture includes an increase of bilirubinemia and liver enzymes, and the presence of coagulopathy. A progressive destruction of small intrahepatic bile ducts, that conduces to vanishing bile duct syndrome and, sometimes, to end-stage liver disease, appears in chronic liver GVHD [4].

Between the complications that appeared after allogeneic peripheral stem cell transplantation, chronic GVHD is the main case of poor long-term outcome and quality of life [3].

Persistent GVHD together with chronic hepatitis C, cirrhosis and hepatocellular carcinoma are the main liver entities found in the longest-lived survivors of hematopoietic stem cell transplantation [5].

EPIDEMIOLOGY

Up to 80% of patients subjected to allogeneic peripheral stem cell transplantation develop liver-related complications, which substantially contribute to their overall morbidity and mortality. They can appear during the first 100 days, as preengraftment phase complications (in the first 30 days after transplantation) and early posttransplantation phase complications (between 31 and 100 days after transplantation) [6] (drug-induced liver injury [7], acute GVHD, or sinusoidal obstruction syndrome [6, 7], hemorrhagic cystitis, neutropenic colitis, benign pneumatosis [6]) or after the first 100 days (infectious sequelae, cirrhosis, liver tumors [7], chronic GVHD or lymphoproliferative disease [6]).

Acute GVHD occurs in up to 30-50% of patients who were subjected to human leucocyte antigen-matched sibling transplants [8]. But this percentage can vary in different studies. Thus, a percent of 8.2% of a group of 170 patients who received an allogeneic peripheral stem cell transplant,

where the donors were 6/6 HLA-matched siblings, developed grade II-IV acute GVHD, and 81.2% of them – chronic GVHD. Fifty-seven percent of patients had liver involvment in the same study [9]. Chronic GVHD appears in at least 30% to 50% of patients who underwent a transplant from human leukocyte antigen matched siblings and at least 60% to 70% of recipients of grafts from unrelated donors [3]. The incidence of chronic GVHD was 70% in a series of 171 patients who received an allogeneic peripheral blood stem cell transplantat; it was mild in 29%, moderate in 42%, and severe in 28% of them [10]. About 50% of patients with chronic GVHD have limited disease and a good prognosis. Approximately 60% of those with extensive disease will evolve favourably under treatment and eventually be able to stop immunosuppressive treatment [3].

More patients developed chronic GVHD and were under immunosuppressive treatment 5 years after allogeneic peripheral blood stem cell transplantation (with more often involvement of skin, liver, and oral mucosa) comparing with those who received a bone-marrow transplant. These differences do not affect general health status, survival or late events more than 9 years after the allograft [11].

PATHOPHYSIOLOGY

Acute GVHD and early endothelial injury syndromes

Acute GVHD has common features with the entities included in early endothelial injury syndromes, which are: liver sinusoidal obstruction syndrome (previously known as veno-occlusive disease), transplant-associated microangiopathy, diffuse alveolar hemorrhage, capillary leak syndrome, and engraftment syndrome, whose occurrence is more frequent after allogeneic hematopoietic stem-cell transplantation with non-T-cell-depleted grafts or in unrelated transplantation. The patients with endothelial form of acute GVHD are likely to develop these mentioned entities. The infiltrate with alloreactive cytotoxic T lymphocytes is responsible for the rarefaction of microvessels, which can be found in chronic GVHD. There are observations that support the existence of a common denominator in the pathogenesis of vascular endothelial GVHD, early endothelial damage syndromes and atherosclerosis. An immunological mechanism seems to be also involved in the pathogenesis of atherosclerosis [12].

Cytosolic glutathione S-transferase

The enzymes of cytosolic glutathione S-transferases family are involved in the catabolization of busulfan and the metabolites of cyclophosphamide, after their conjugation with glutathione. It is important to know the single nucleotide polymorphisms in the promoter region of the glutathione S-transferase A1 gene of patients who received a busulfan/cyclophosphamide conditioning regimen, due to the fact that glutathione S-transferase A1 gene *A/*A diplotype is an independent protective factor against acute GVHD (only 15.2% of patients with this diplotype developed a grade II-IV acute GVHD, compared to 40.0% of patients with other diplotype) and probably for liver GVHD (only 13% had this pattern of GVHD, compared to 27% in patients without this diplotype). This could be a criterion for choosing the type of conditioning regimens and to change the prophylaxis of GVHD [13]. The appearance of liver acute GVHD, especially its acute form, was associated with the glutathione S-transferase T1 (GSTT1) – mismatch and the presence of anti-GSTT1 antibodies in post-transplant period. The authors believe that GSTT1 could be considered as a new minor histocompatibility antigen in liver GVHD [14].

Immune tolerance

It is accepted that the use of peripheral blood mobilized stem cells contributes to increase the risk of chronic GVHD and prolonges the duration of immunosuppression. The immune tolerance present after stem cells allograft supposes a state of immune quiescence with reduced expression of costimulation and immune response genes, while the cell cycle control genes are upregulated. There are data supporting indirectly the main role of tumor growth factor-beta and CD4(+)CD25(+) regulatory T cells, and provides new insights concerning the role of natural killer cells. GammadeltaT cells (including the selection of the Vgammadelta1+ subtype) have an important role in the mechanism of liver tolerance against the allograft. Understanding and finding markers for immune tolerance will allow a better management of immunosuppressive therapy after allograft, which is currently empirical [15].

GVHD – cause of immunosuppression

In an experimental study, mice with and without chronic GVHD were injected with a non-lethal dose of murine cytomegalovirus at 100 days after allograft. The animals affected by chronic GVHD had higher viral loads in the liver and spleen and more weight loss. This is proof that GVHD is an important cause of immunosuppression which explains the functional immunodeficiency present in allografted recipients [16].

The role of donor-derived hematopoietic cells in the liver

Nine female patients were treated by allogeneic bone marrow or peripheral stem cell transplantation from a male donor. In their liver there were found 5.6-fold more Y-chromosome-positive than CD45-positive staining cells (especially in patients who had developed GVHD), an argument for the idea that donor-derived hematopoietic cells appeared to turn in mesenchymal liver cells [17]. Donor T-cells accompanied by CD25 expression seem to migrate to lymphoid organs (including the spleen and liver) to induce GVHD lesions in a mice model of hematopoietic stem cell transplantation [18]. Activated CD4(+) T cells are involved in GVHD development. But they also mediate the production of antibodies. A pilot study found that C4d expression was increased in portal vessels and hepatic sinusoids of patients with histological proven liver GVHD, fact that highlights the role of humoral activation in this process [19].

Contribution of experimental models of GVHD to understanding its pathophysiology

In a mouse model of GVHD induced by parental spleen CD4(+) T cell injection, administration of anti-IL-10 antibody in advance and in maintenance treatment for 2 weeks led to a lack of Tr1 cells detection with a significant aggravation of inflammation, due to the fact that regulatory T cells (especially the Tr1 cells) had been reported to control excessive immune response and prevent the diseases with immune pathogenesis [20].

An experimental murine model of cyclosporine A – induced syngeneic GVHD leads to the development of both chronic colon and liver inflammation. Intra- and extrahepatic bile ducts lesions, increased levels of mRNA for the chemokines CCL25, CCL28, CCR9, and T(H)1- and T(H)17-associated cytokines, and mucosal cellular adhesion molecule -1. CD4(+) T cells were found in the peribiliary region of the liver of animals with syngeneic GVHD. This model is useful to study the entero-hepatic linkage between the two sites of inflammation [21].

In another experimental mice model of acute GVHD, halofuginone, that selectively inhibits Th17 differentiation and facilitates Th1 differentiation [22] contributed to the augmentation of liver and and small intestine GVHD, due to the fact that early blockage of Th17 cell conduced to an increased percentage of Th1 cell [23]. In acute GVHD there is a Th1/Th17 imbalance, that positively correlates with its severity. An increased Th1-type reaction is responsibe for an aggravated liver GVHD [22].

Also in a murine model of GVHD, CD4(+) T-cell (Th) 1 was the most frequent subset of Th along the entire duration of the disease, but its frequencies decreased over time. The highest pathologic GVHD score of the liver was at day +28 and it began to improve at day +56, when Th17 cells emerged (they were rarely detected formerly) along with an improvement of liver inflammation. Thus, an association of attenuation on chronic GVHD with a later emergence of Th17 cells and concomitant decrease of Th1 [24] was shown.

The use of granulocyte colony-stimulating factor

A severe chronic GVHD was observed after the use of granulocyte colony-stimulating factor for peripheral blood stem cells mobilization in donors, as a consequence of the transfer of numerous donor T cells in conjunction with a supposed expanded myeloid lineage. In the recipients of control grafts the severity of liver chronic GVHD was reduced [25]. The mobilization of stem cells with pegylated granulocyte colony-stimulating factor contributes to the modulation of donor T- and natural killer T-cell functions, thereby separating GVHD from graft-*versus*-leukemia disease in experimental studies on animal models. As side effects, a late transient increase in serum liver transaminases was noted; the others were similar to those observed in donors mobilized with standard granulocyte colony-stimulating factor [26].

The role of cytokines

Tumor necrosis factor (TNF) is a cytokine with an important role in the production of GVHD.

In an experimental mice model of liver GVHD, an adenovirus encoding a TNF receptor inhibitor or beta-galactosidase was used. The result was a reduction of GVHD-induced "wasting disease" and of the number of liver CD8(+) T cells after TNF inhibitor introduction, compared to beta-galactosidase adding, and of both individual venulitis and composite histopathological scores (also after this cytokine inhibitor). Therefore, the use of an adenovirus encoding a TNF receptor inhibitor could be a solution to reduce the severity of liver GVHD [27].

Studying the expression of 30 chemokines or chemokine receptors in an experimental model of acute GVHD in mice, it was shown that hepatic CXCR3 expression did not change, but a clear association was observed for CXCL16 and CXCR6 expression. The liver expression of CCL3-CCL5 was associated with an increase of CCR1 and CCR5. The hepatic expression of CCL2, CCL8, CCL12 and their receptor CCR2 were also increased [28]. CCR5 is a CC chemokine receptor. It was shown a greater degree of hepatic pathological changes in mice that received a graft knock-out of CCR5 on donor cells. T cells recovered from recipients of CCR5 KO cells produced more TNF-alpha and IFN-gamma and proliferated more frequently to a T-cell than T cells from recipients of WT cells. An increase of GVHD and donor CD8(+) T cell expansion were seen after the graft with knock-out of CCR5 on donor cells [29].

It was shown that NR58-3.14.3, an extensive spectrum chemokine inhibitor, can suppress leukocyte migration (including that of mononuclear cells) in response to different chemokines, including CCL2, CCL3, CCL5. Given in an experimental mouse model, NR58-3.14.3 was able to reduce the acute liver GVHD, with a decrease of hepatic cellular infiltrates [30].

How to explain histopathological lesions?

Ductopenia and apoptosis of epithelial cells of small- to medium-caliber bile ducts is a consequence of T-cell infiltration found in non-suppurative destructive cholangitis – the morphological process that exists in GVHD, hepatic allograft rejection and primary biliary cirrhosis. This process is preceded by liver synthesis of pro-inflammatory cytokines, and expression of chemokine genes and amassment of lipopolysaccharide [31]. In a murine model of liver GVHD, pro-inflammatory cytokines (in particular TNFα and IFNγ) were involved in the induction of immortalized biliary epithelial cells gene expression and the secretion of chemokine ligands for the following chemokine receptors CCR1, CCR3, CCR5, and CXCR3. These chemokines chemoattracted activated T cells. The fact that non-suppurative destructive cholangitis is limited to small-to medium-caliber bile ducts could be explained by selective chemokine expression at this level [31].

Complement activation

Complement activation also takes part to GVHD development. Thus, in a murine model of acute GVHD it was established that excessive complement activation (C3a and C5a as well as their receptors C3aR and C5aR1) was involved in this pathological process. The liver content of C3a and C5a was increased substantially and deposits of C3 were seen in hepatic portal areas, with massive inflammatory cell infiltration around them [32].

GVHD as treatment of various cancers

Reduced-intensity allogeneic peripheral blood stem cell transplantation is sometimes used as salvage therapy in various cancers which were resistant to conventional chemoradiotherapies, as it happened in a patient with advanced colon cancer. He obtained a complete donor-type chimerism, but afterwards he developed a severe liver GVHD (with hyperbilirubinemia), apparently accompanied by graft-*versus*-tumor effect which, although it did not allow to obtain complete remission, resulted in a stable disease condition for 18 months [33].

CLINICAL AND LABORATORY FINDINGS

A timely and accurate diagnosis of GVHD is necessary for the success of the treatment [34]. The acute GVHD can evolve towards chronic GVHD, but the latter may occur by itself or subsequent to recover after acute GVHD [3].

Pre-engraftment GVHD

In a series of 384 patients who were treated by allogeneic cell transplantation, 100 developed acute GVHD, that appeared only in 22 patients in the pre-engraftment period. This pre-engraftment GVHD was more severe and evolved more frequently with liver dysfunction, higher cumulative incidence of non-relapse mortality and lower

overall survival compared to those without acute GVHD. This pre-engraftment GVHD seems to be a 'cytokine storm' type syndrome [35].

The main clinical and laboratory manifestations

From the clinical point of view, liver GVHD which appears after allogeneic hematopoietic stem cell transplantation manifests by cholestatic jaundice and increased serum values of alkaline phosphatase. Serum bilirubin levels allow to estimate the GVHD severity [36]. The presence of liver injury, defined as an incease of total bilirubin level, at 1 month after allogeneic hematopoietic stem cell transplantation, led to a transplantation-related mortality of 60.7% at 1 year compared with 14.6% in patients without liver injury. The risk factors for the apeareance of liver injury at 1 month are the age, pre-transplant total body irradiation, invasive fungal infection and bacterial bloodstream infection, according to a multifactorial analysis [37]. The multivariate analysis of data from enrollment visits and all visits, obtained from Chronic GVHD Consortium observational cohort study, established that elevated bilirubin was associated with overall survival, nonrelapse mortality and quality of life [38].

After donor lymphocyte infusion it was shown an important increase of aminotransferases, without hyperbilirubinemia, that mimicked an acute hepatitis. The histopathological study of liver biopsies can establish the right diagnosis in these cases [36].

The appearance of eosinophilia in an allogeneic bone marrow transplanted patient could be a manifestation of acute GVHD [39]. But 44% of patients presented eosinophilia ($\geq 0.5 \times 109/L$) at diagnosis of chronic GVHD, too. This diagnosis was established after a median time of 4.5 days after the onset of eosinophilia. A lower prevalence of eosinophilia in this allograft complication was associated with thrombocytopenia [9].

High percentage of schistocyte can be found in acute or chronic GVHD, but also in cholestatic hepatitis, sinusoidal obstruction syndrome, haemorrhagic cystitis and pulmonary complications. A mild augmentation advocates for extensive endothelial damage while higher percentage of schistocyte requires investigations and a close monitoring of stem cell transplantation thrombotic microangiopathy [40].

Serum cholesterol and triglycerides rose from normal values before GVHD to 1,122 mg/dL and 1,100 mg/dL, respectively, in a case of severe liver GVHD, due to the fact that intra-hepatic cholestasis produced a reflux of bile lipoproteins into the blood flow and subsequent formation of lipoprotein X, which mediated this increase [41].

The CD4(+)interleukin (IL)-4(+) T cell frequency, the kinetics of CD4(+)interferon (IFN)-γ(+) T cell, and and the plasma level of IFN-γ and IL-10 seem to coincide with the activity of GVHD. They are higher during the acute or chronic GVHD development. Especially IL-10 correlated with the activity of GVHD during immunosuppressive treatment and the severity of liver GVHD [42].

The role of radiological examinations

Abdominal radiologic imaging and intervention are important for an early, minimally invasive diagnosis and treatment of GVHD. Although imaging findings are frequently nonspecific, they can guide further management. Image-guided transvenous hepatic biopsy may be safer than those performed transcutaneous [34].

Histopathological aspects

The following liver histopathological aspects of GVHD can often be found: active hepatitis characterized by portal and diffuse lobular inflammatory infiltrate [27, 43], venulitis and bile duct inflammation [27]. But the most characteristic histopathological aspect is the presence of small bile duct damage [43, 44], which may be severe [44]. In the literature, there are also some cases of marked lobular hepatitis and hepatocellular damage, labeled as "hepatitic GVHD": in a series of 6 pediatric patients liver GVHD appeared between 149 and 310 days post-transplant and was manifested by bile duct epithelial damage and significant portal/periportal inflammation (in all patients) and lobular necro-inflammation (in 5 of them) [44] and in other 3 patients there was a marked elevation of serum aminotransferases, clinically suggesting an acute viral hepatitis [43]. Sometimes, a lymphocytic infiltration of the portal tracts and lobular pericentral necrosis coexisted with a picture of periductal lymphocytic infiltration and vacuolization of the biliary epithelial cells, aspect which was compatible with a "cholangiohepatitic type of GVHD". This pattern of liver GVHD presentation should be considered in peripheral stem cell allografted patients, including after donor lymphocyte infusion, if they develop an increase of aminotransferases [36].

The histopathological examination of oral mucosa or lip salivary glands, even in the absence of clinical oral symptoms of GVHD, is useful for

the diagnosis of GVHD, which has been confirmed in 9 of 12 patients with liver GVHD. They presented mild lymphocytic infiltrates and apoptotic bodies in oral mucosa, and mild inflammatory infiltrates with minimal CD8(+) T cells predominance in the invaded ducts epithelium in lip salivary glands [45].

DIFFERENTIAL DIAGNOSIS

Increased liver enzymes

High serum level of liver enzyme can be found after allogeneic stem cell transplantations not only in GVHD or drug-induced liver injury, but also in acute hepatitis E virus (HEV) infection, which can progress to chronicization in these immunosuppressed patients. The screening of this infection could be useful in allografted patients with liver cytolysis, but also in donors who have liver dysfunction. There is a discussion on HEV screening of blood products [46] concerning the cost-effectiveness ratio.

Caspase-cleaved neo-epitope of cytokeratin-18 fragments

Increased serum levels of caspase-cleaved neo-epitope of cytokeratin-18 fragments can be found in active GVHD, as an expression of induced target organ destruction, but it is not elevated in noncomplicated, infection-related diarrhea, toxic mucositis, and sinusoidal obstruction syndrome [47].

Human leukocyte antigen DR surface expression of CD14+ monocytes

The study of the expression level of the human leukocyte antigen DR surface expression of CD14+ monocytes can be useful in various situations: it increases during or before acute GVHD and at the time of viremia, and decreases in sinusoidal obstructive syndrome, prior and during bacterial infection or sepsis, in case of relapse of the underlying disease and before death [48].

Anti-mitochondrial antibodies

The presence of anti-mitochondrial antibodies in a patient with chronic GVHD should raise the suspicion of primary biliary cirrhosis. Histopathology can contribute to the diagnosis of these associated diseases [49].

The role of computed tomography (CT) scan

Sometimes, CT scan could be useful to distinguish between liver GVHD and sinusoidal obstruction syndrome: for the first advocates a small-bowel wall thickening, and the second is more likely in the presence of ascites, periportal edema, and a narrow right hepatic vein [50].

Main histopathological lesions

Besides acute and chronic GVHD, where damaged hepatocytes and small bile ducts can be found, there are also other liver complications after haematopoietic stem cell transplantation, such as: sinusoidal injury (due to myeloablative conditioning regimens), biliary symptoms (as a result of microcrystalline deposits in the gall bladder), drug-induced liver injury (occurs frequently), and various infections with liver tropism (especially viral and fungal), during the period of severe immune suppression [51].

High liver iron deposits

Frequently, the patients who are subjected to hematopoietic stem cell transplantation have a history of red blood cell transfusions. These and peritransplant events explain their increased iron stores [52]. Anecdotal data suggest that even if histopathological examination of liver biopsies showed the presence of GVHD and concomitant excessive iron overload [53], these iron deposits can mimic a chronic GVHD [52] or its exacerbation [53]. For these patients the treatment with iron chelators and phlebotomy (including a maintenance phlebotomy program) and not continuation or intensification of immunosuppressive therapy for GVHD ensures them a favorable evolution [53].

RISK FACTORS

The role of liver dysfunction

In a recent single-center retrospective study it was shown that 19.8% of patients had liver dysfunction before receiving the allogeneic hemato-

poietic stem cell transplantation and 81.1% of them had liver dysfunction during conditioning (28 from 192 presented grade 3 liver dysfunction). This pre-transplant or during conditioning liver dysfunctions seems to have no influence on the acute or chronic GVHD. These liver dysfunctions appeared before transplantation or during conditioning period and do not seem to affect overall survival rate and transplant-related mortality rate, too [54]. Instead, the use of etoposide in the preparative regimen and the acute hepatic GVHD are risk factors of death due to chronic GVHD after allogeneic hematopoietic peripheral stem cells transplantation [55].

Main risk factors

The main risk factors for chronic GVHD are high age of patient or donor, previous acute GVHD, use of peripheral stem cells rather than hematopoietic marrow, higher degree of histoincompatibility, unrelated *versus* related donor, donor leukocyte infusions, nonmyeloablative conditioning regimens [3].

Between the factors that affect overall survival rate and transplant-related mortality rate is also grade III-IV liver acute GVHD [54]. Apart from a history of acute liver GVHD, a platelet number below 100,000/mm^3 is another predictive factor for poor survival after at least 100 days since the allogeneic hematopoietic peripheral stem cells transplantation [55]. A severe form of chronic GVHD adversely influenced outcome, according to scoring system proposed by the National Institutes of Health, but *de novo* onset had a more favorable impact on survival [10].

A single center study made on 255 patients at day +100 after allogeneic hematopoietic stem cell transplantation, with a graft obtained from an HLA-identical sibling or a matched unrelated volunteer, established that the risk for nonrelapse mortality was 10% if pateints had hyperbilirubinemia, 22% for hypoproteinemia alone, and 70% when hyperbilirubinemia and hypoproteinemia were both present (which are a consequence of liver and intestine functions impairment) [56].

The presence of GVHD is an important risk factor for venous thromboembolic events after stem cell transplantation and pre-existing liver damage is a risk factor for sinusoidal obstructive syndrome, where a hepatic venous pressure gradient over 10 mmHg is highly specific [57].

MARKERS OF GRAFT *VERSUS* HOST DISEASE

A *high hepatic artery resistance index* (≥0.74) before allogeneic stem cell transplantation could be an important predictor of significant liver GVHD in patients after the allograft [58].

It was shown that *liver function tests* and *the number of lymphocytes* at day +100 are predictive factors for severe and extensive chronic GVHD after allogeneic peripheral blood stem cell transplantation [59].

A *serum IL-18 increase* of at least 1.6-fold after engraftment is associated with acute grade II GVHD or higher with a sensitivity of three out of four. This "cut-off" allows to reach a specificity of up to 100% [2].

A histopathologic hallmark of GVHD is *the presence of apoptosis*. It was shown that serum levels of the caspase-cleaved neo-epitope of cytokeratin-18 fragments decreased if patients with active GVHD responded to immunosuppressive therapy and had persistent high values if they did not respond. This marker, which reflects active GVHD-induced target organ destruction, can be used for differential diagnosis and monitoring the evolution of GVHD [47].

Liver GVHD was less severe in mice without *growth arrest-specific gene 6* in endothelial cells. This absence impaired donor T-cell transmigration into the liver [60].

CONCLUSIONS

After the skin, the second most frequent organ affected by GVHD is the liver.

Graft *versus* leukemia or lymphoma reaction is the beneficial component of graft *versus* host disease, whose appearance would be stimulated (if it does not appears spontaneously).

An aggressive GVHD can be a life-threatening disease.

Careful assessment of liver function during pre-graft balance and GVHD prophylaxis are essential steps in order to avoid a severe GVHD.

The main manifestations of liver GVHD are increasing serum bilirubin and alkaline phosphatase (and sometimes of liver enzymes) level, the presence of coagulopathy, non-suppurative destructive cholangitis, portal and diffuse lobular inflammatory infiltrate and venulitis.

The presence of liver injury, defined as an increase of total bilirubin level, at 1 month after allogeneic hematopoietic stem cell transplantation

led to a transplantation-related mortality of 60.7% at 1 year [37].

Liver function tests and the number of lymphocytes at day +100 are predictive factors for severe and extensive chronic GVHD after allogeneic peripheral blood stem cell transplantation [59].

Future studies on better understanding of the immune mechanisms, of the interaction between different components that contribute to GVHD, the influence of genetic and gene expression profiling of different patients may contribute to better understanding and more effective therapeutics solutions finding to this complication.

Conflicts of interest: The author declares no conflict of interest.

Reacția grefă contra gazdă (RGCG) este cea mai importantă complicație a transplantului alogeneic de celule hematopoietice şi este mai frecventă după transplantele de celule stem periferice. Componenta ei de reacția grefă contra leucemie sau limfom este benefică pentru eradicarea masei tumorale reziduale după tratamentul şi regimul de condiționare a grefei efectuate anterior. O RGCG severă poate periclita viața pacientului. Cele mai importante manifestări hepatice ale RGCG sunt valorile serice crescute ale fosfatazei alcaline serice şi ale bilirubinei. Ultima permite estimarea severității RGCG. Uneori, o creştere a aminotransferazelor poate mima o hepatită acută. Celule hematopoietice provenite de la donator par să se transforme în celule hepatice mezenhimale. Celulele T CD4(+), activarea umorală şi cea a complementului, un număr mare de citokine şi de receptori citokinici sunt implicați în producerea RGCG. Recunoaşterea timpurie şi corectă a RGCG şi diferențierea ei de alte hepatopatii sunt esențiale pentru practica medicală.

Correspondence to: Professor Romeo-Gabriel Mihăilă
Faculty of Medicine, Str. Lucian Blaga, 2A, 550169, Sibiu, Romania
Phone: +40269 215050. Fax: +40269 218365.
E-mail: romeomihaila@yahoo.com

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