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Review

Allogeneic hematopoietic cell transplant in HCV-infected patients☆

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Hepatitis C virus (HCV) is a major cause of liver disease worldwide. After allogeneic Hematopoietic Cell Transplant (HCT), HCV is known to be associated with transient hepatitis in the immediate post-transplant period, and a potential risk factor of veno-occlusive disease (SOS). Very recently, HCV-infected HCT recipients have been shown to be at higher risk of earlier cirrhosis, leading to greater morbidity and mortality. Long-term survivors after HCT are thus at a high risk for HCV-related complications and, as a consequence, the treatment of HCV infection becomes critical. We describe here the potential clinical complications in HCV-infected recipients, in the short, but also the long-term follow-up after HCT. The pathophysiology of liver fibrosis is discussed as well as the present recommended therapy in this particular population.

***Keywords*: Bone marrow transplantation; Long-term outcome; Cirrhosis; Antiviral treatment HCV**

1. Introduction

Allogeneic Hematopoietic Cell Transplant (HCT) has now become a widely used therapeutic procedure to cure patients with malignant and non-malignant hematological disorders. Nearly 90% of the patients, who remain recurrence-free of their original disease more than 2 years after the procedure, are expected to become long-term survivors, leading to thousands of cured patients worldwide [1].

Liver complications influence morbidity and mortality in patients undergoing HCT. Liver injury is common early after HCT because of veno-occlusive disease (SOS), Graft-versus-Host Disease (GVHD), drug toxicity, post-transplantation viral hepatitis and disease relapse [2–4]. Among the long-term complications, cirrhosis is an important late complication of HCT [5].

The hepatitis C virus (HCV), identified in 1989, is an enveloped Flavivirus with a 9.6 kb single strand RNA genome [6]. A significant proportion of long-term HCV-infected HCT survivors, primarily contaminated through blood exposure, develop cirrhosis and hepatocellular carcinoma during long-term follow-up [5,7]. Moreover, HCT recipients showed a higher rate of liver fibrosis progression as compared with HCV-infected patients who did not receive a transplant [7]. We describe here the natural history of HCV infection in the early period as well as during the long-term follow-up after HCT. We discuss the potential reasons related to the higher fibrosis rate in transplanted patients and the anti-HCV therapy of this particular population.

2. Blood exposure

Hepatitis C virus (HCV) is a major cause of liver disease worldwide. HCV is the most common chronic blood–borne infection in the United States. The Centers for Disease Control estimated that during the 1980s, an

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Abbreviations: Graft versus Host Disease (GVHD); Allogeneic Hematopoietic Cell Transplant (HCT); Hepatitis C Virus (HCV); Sinusoidal Obstruction Syndrome (SOS); Interferon (IFN); Ribavirin (RBV); Interleukin 1 (IL-1); Tumor necrosis factor alpha (TNFα).

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average of 230 000 new infections occurred each year. Although the annual number of new infections has declined by more than 80% since the 1990s, population-based studies indicate that 40% of chronic liver diseases are HCV-related. HCV is transmitted primarily through blood exposure. However, blood transfusion, which accounted for a substantial proportion of cases of HCV infections acquired more than 10 years ago, rarely accounts for recently acquired infections owing to systematic screening of blood products for HCV [8–11].

While the risk of acquiring HCV infection is now extremely low, it is not uncommon that patients come to HCT already infected. Moreover, a large group of long-term stem cell survivors were infected by HCV during the 1980s before blood donors were routinely screened. Indeed, prospective studies of transfusion recipients in the United States demonstrated that the rates of post-transfusion hepatitis in the 1970s exceeded 20% [9]. For instance, in Seattle, WA, HCV was detected after HCT in 113 of 355 (32%) patients in 1987–1988 [5,12]. A recent prospective study of the European Group for Blood and Marrow Transplantation, which included patients who received transfusions in the "postscreening" era, showed that the prevalence of HCV RNA-positive stem cell transplant recipients was 6.0% [13]. Thus, chronic hepatitis C in long-term survivors remains an important clinical issue.

3. HCV diagnosis in the context of HCT

Virological diagnosis of HCV infection has evolved with time. At the end of the 80s, the first-generation assay that became available was able to detect antibodies against a blood–borne non-A, non-B hepatitis virus termed HCV [14,15]. The clinical relevance was controversial in the non-transplanted population since unspecific reactivity can occur with sera in some categories of patients [16]. The introduction of a second-generation test and the use of supplementary tests such as RIBA have improved the reliability of serologic assays. The clinical relevance of positive HCV antibodies in HCT patients was still questionable. It has thus been shown that highly immunosuppressed patients may have a defect in producing antibody [17,18]. HCT recipients are usually not able to mount a serologic response to virus infections during the first year after transplant. Moreover, positive HCV antibodies may be the consequence of passive antibody transfer by transfusion, in the absence of preceding viremia. Those methods were largely used as diagnosis in many studies after HCT leading to under- (lack of specificity) or over-estimation (lack of sensibility) of HCV-infected HCT patients. In the beginning of the 1990s, the direct detection of HCV by polymerase chain reaction (PCR) allowed to estimate the true frequency of HCV infection in blood donors [19,20]. As was predictable, studies reported patients who were PCR-positive and negative by serologic tests, notably in the period following HCT [21,22].

Regarding assays to detect HCV antibodies, the specificity of third generation EIAs is greater than 99% [23]. Their sensitivity is more difficult to determine, given the lack of a gold standard method, but it is excellent in HCV-infected immunocompetent patients. HCV-RNA testing is still helpful in patients with immune depression clinical or analytical suspicion of liver disease [24,25], notably after HCT [12].

4. HCV-infected HCT recipients and clinical outcome

4.1. Short-term outcome

In the first three months after transplant, liver dysfunctions related to HCV are usually mild [12,22,26,27] limited to 5- to 10-fold increase in alanine aminotransferase (ALT) [22]. Several causes of liver dysfunctions are present at this time (2–4). The main problem during this period is to differentiate between acute GVHD and hepatitis. Unless there is evidence of active GVHD in other organs, a liver biopsy is usually needed before a therapeutic decision is made. Pathologic distinctions between HCV and GVHD may be difficult, as both are associated with portal lymphoid infiltration and bile duct injury. Nevertheless, marked bile duct injury with epithelial cell drop-out and loss of interlobular bile ducts are more typical of GVHD [12,28,29]. After three months, the occurrence of late hepatitis is possible, which coincides with a decrease in or discontinuation of immunosuppressive therapy and a return of cellular immunity [12,13,26,30,31]. The most difficult situation at this time is the unusual presentation of liver GVHD (hepatic Variant), resembling viral hepatitis [32,33], also described after donor lymphocyte infusion [34], in which liver biopsy is essential to confirm GVHD.

4.2. HCV and hepatic sinusoidal obstruction syndrome (SOS)

Veno-occlusive disease has been recently renamed hepatic sinusoidal obstruction syndrome (SOS) [35,36]. SOS is a liver toxicity syndrome after BMT caused by occlusion of centrilobular venules and damage to the surrounding hepatocytes and sinusoids, after myeloablative conditioning regimen [36,37]. SOS of the liver is characterized by hyperbilirubinemia, fluid retention, and painful hepatomegaly appearing soon after BMT [36,38]. Individual variability in cyclophosphamide metabolism, total body irradiation (TBI) dose, use of

gentuzumab ozogamicin and pre-existing liver inflammation and fibrosis are risk factors [12,39–41].

The potential role of HCV in the development of SOS remained for a long time a matter of debate in the literature, as illustrated in the Table 1. The role of HCV a risk factor for fatal SOS was identified in a cohort of patients who received cyclophosphamide or TBI over 12 Gray, related to sinusoidal toxins of those regimens. HCV is thus not considered as a risk factor if the conditioning regimen has little or no liver toxicity such as fludarabine and targeted busulfan [42,43] or non-myeloablative regimen of fludarabine plus low-dose TBI [44]. An informative review on management of hepatic disease following haematopoietic cell transplant has been published recently [45].

4.3. Long-term outcome (Table 2)

For a long time, HCV infection was not considered as a major problem after HCT. Studies appeared concomitantly demonstrating the ability to identify antibodies directed against HCV [14,15]. In 1991, Locasciulli et al. found an overall prevalence of positive HCV antibodies of 28.6% (38/128 patients) which was not correlated with more severe liver disease after HCT. Nevertheless, pathological findings demonstrated more severe liver damage in patients with HCV-positive antibodies. A chronic hepatitis was thus diagnosed in 9 out of 11 patients presenting antibodies against HCV while in only one patient out of 7 who did not have positive HCV antibodies [46]. Further studies were more attentive to the risk of acquiring HCV infection in the context of HCT than to determine the role of HCV in post-transplant liver complications [47–49]. Moreover, Norol et al. showed that HCV-positive antibodies before and after HCT were not predictive of SOS, liver GVHD, or death due to liver dysfunction. In contrast, the risk of chronic hepatitis was significantly increased [49]. The first study which directly assessed the impact of HCV infection in long-term survivors after HCT was conducted by Ljungman et al. [22]. The diagnosis was based on the HCV positivity either by PCR for HCV-RNA or by second-generation enzyme-linked immunoabsorbent assay (ELISA) and RIBA or EIA supplemental assay. Of 161 surviving patients transplanted between 1978 and 1991, 28 (17.4%) were found to have chronic HCV infection. No signs of severe progressive liver disease were shown among the patients included in this study with a follow-up median time of 6.1 years [22]. Thomas et al. with an average follow-up of 6 years found no evidence of cirrhosis [50]. In 1999, the Seattle group reported a cohort of 355 patients that underwent HCT between 1987 and 1988 from which 113 (32%) were HCV RNA-positive by day 100 post-transplant. During 10 years of follow-up, no patients developed clinical evidence of liver disease, and HCV infection did not impact the actuarial survival of long-term survivors over this time period [12]. It was thus concluded that HCV infection was not associated with excess mortality over ten years of follow-up.

However, the same group observed the development of cirrhosis leading to hepatic decompensation and hepatocellular carcinoma in HCV-infected, marrow transplant recipients, surviving beyond 10 years. Among 3721 patients who survived 1 or more years after HCT, 31 developed cirrhosis. Cirrhosis was attributed to HCV in 15 of 16 patients presenting more than 10 years after HCT [5]. In our experience, 15 patients among 96 HCT, HCV-infected recipients (diagnosed by RT-PCR), developed biopsy-proven cirrhosis at a median follow-up of 15.7 years, leading to a cumulative incidence of cirrhosis of 24% at 20 years. HCV infection ranked third, behind infection and GVHD, as a cause of late death. Moreover, cirrhosis was diagnosed beyond 10 years after transplantation in 13 of our 15 patients. We thus observed 3 cases of hepatocellular carcinoma [7]. Ivantes et al. also found cirrhosis on a smaller group of patients followed up more than ten years after HCT [51]. Thus, HCT recipients with HCV infection present a higher risk of earlier cirrhosis.

HCT, HCV-infected patients thus present a higher risk of earlier cirrhosis in the long-term follow-up.

Table 1
HCV and the risk of SOS

Sources	Year	HCV-infected patients[#]	SOS after transplant[§]	HCV as a SOS risk factor
Frickhofen et al.	1994 (retrospective)	6/61	5/6 versus 9/52[*]	Yes ($p < 0.005$)
Ljungman P et al.	1995 (prospective)	10/161	1/10 versus 12/133[**]	Non-significant
Rodriguez-Inigo E et al.	1997 (prospective)	11/58	2/11 versus 7/46[***]	Non-significant
Locasciulli et al. (*EBMT*)	1999 (prospective)	11/193	1/11 versus 15/170[****]	Non-significant
Strasser et al.	1999 (prospective)	62/355	22/46 evaluable patients versus 32/229[*****]	$p < 10$–3 if associated with elevated AST before transplant

Abbreviations: [#]Number of HCV-infected patients before transplant versus total number of patients. [§]Number of SOS among HCV-infected patients versus number of SOS among HCV-negative recipients. [*]Three patients were infected during or shortly after BMT. [**]Eighteen patients were infected during or shortly after BMT. [***]One patient was infected during or shortly after BMT. [****]Twelve patients were infected during or shortly after BMT. [*****]Fifty-two patients developed HCV infection during the HCT process; only severe SOS is depicted.

Table 2
Retrospective analysis of HCV infection in the long-term follow-up after *HCT*

Sources	Year	Number of HCV patients	HCV diagnosis	Median follow-up (years)	HCV-related complications
Locasciulli et al. [46]	1991	38/128	Serology	2	Hepatitis exacerbation after *HCT* More severe liver damage (biopsy) in anti-HCV+ patients
Norol et al. [49]	1994	14/120	Serology	Not given	More chronic liver disease in HCV+ patients
Ljungman et al. [22]	1995	28/161	Serology and PCR	6.1	No difference according to HCV status
Strasser et al. [12]	1999	113/355	PCR	10.4	No difference according to HCV status
Thomas et al. [50]	2000	29/61*	Serology and PCR	6	No increase of morbidity or mortality
Peffault de Latour et al. [7]	2004	96/686	PCR	15.7	Fifteen patients with biopsy-proven cirrhosis
Ivantes et al. [43]	2004	31/80	Serology and PCR	Patients studied were alive at least 10 years after *HCT*	Three cirrhosis within the 22 HCV patients studied

*The total number of patients is 106 with 61 patients who had chronic liver disease.

5. Higher rate of fibrosis progression in the context of HCT

5.1. Fibrosis progression in non- transplanted HCV-infected patients

Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen [52,53]. Fibrogenesis is a complex dynamic process, which is mediated by necroinflammation and activation of stellate cells. Liver molecular markers (matrix turnover, cytokines) have been associated with fibrosis progression [54]. The severity of disease varies widely from asymptomatic chronic infection to cirrhosis and hepatocellular carcinoma. The natural history of liver fibrosis is influenced by both genetic and environmental factors [55]. The major factors known to be associated with fibrosis progression are male gender, older age at infection, and excessive alcohol consumption. Hepatic steatosis, obesity, and diabetes may also contribute to more rapid progression of fibrosis [56]. Cryoglobulinemia has also been associated with fibrosis in chronic hepatitis C [57].

5.2. Fibrosis progression after HCT

We observed in a study on 96 HCV-infected HCT patients with a median follow-up of 15.7 years a more rapid rate of liver fibrosis progression in transplanted patients as compared with HCV-infected non-transplanted patients (Fig. 1). All these patients had antibodies against HCV and detectable serum HCV-RNA. The expected median time to cirrhosis in allogeneic bone marrow transplant recipients was about 18 years as compared with 40 years in the control population [7]. Another study also confirmed the higher rate of fibrosis progression in HCT recipients. For the three cirrhotic patients of this last study, the average time between HCT and development of cirrhosis was 13 years [51]. These data coming from retrospective studies, should be considered cautiously.

The classic understanding of the pathogenesis of liver disease is that it is due to the cellular immune response against the virus, specifically that of cytotoxic T lymphocytes, which activates hepatic stellate cells, and, thus leads to liver inflammation and fibrosis. The possible high rate of liver fibrosis after HCT, as well as other patients with depressed cellular immunity (HIV co-infection [58,59] and HCV-infected solid organ transplant recipients [60–63], raises fundamental questions about the pathogenesis of liver injury. If there is a more rapid disease progression, it could suggest that, although some aspects of the immune cellular response are clearly ineffective at clearing virus, they do serve to limit liver damage [64]. The HST population has no liver fibrosis progression risk factors since they were young at the onset of infection and have not consumed alcohol. The viral load does not seem to influence the liver fibrosis in immunocompetent patients but a role is suspected in fibrosis progression in HIV/HCV-co infected patients [65]. The HCV viral load is thus higher (up to 10 times) in immunocompromised patients [66,67]. Maina et al.

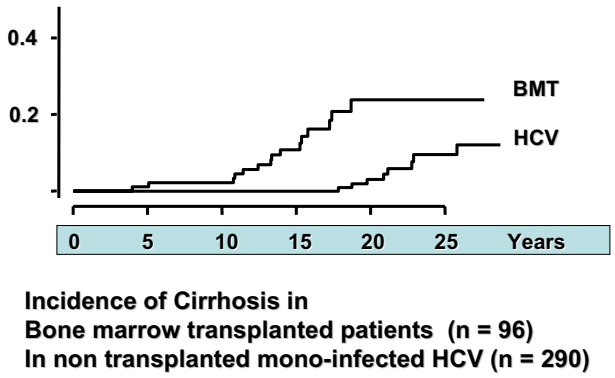

Fig. 1. Cumulative incidences of cirrhosis in chronic hepatitis C patients with stem cell transplant compared to HCV-infected patients without transplantation. Stem cell transplant recipients with chronic hepatitis C ($n = 96$) had an expected median time to cirrhosis of 18 years as compared with 40 years in the control chronic hepatitis C population without transplants ($n = 290$). Ref. [7].

also suggested that a high level of HCV viral load in the immediate period of post-liver transplantation is predictive of more advanced liver disease during the follow-up [68].

In our study, we combined the two patient populations (with and without transplants) and analyzed the risk factors for developing cirrhosis. Only HCT emerged as a significant risk factor by multivariate analysis [7]. Many factors favour liver fibrosis during HCT (Fig. 2). Before transplant, the conditioning alone may support the liver injury, notably TNFα, inflammatory cytokines known to increase liver fibrosis [69]. Iron overload is frequent after HCT, first, because of up-regulation of intestinal iron transport, and second, because of transfusions [70]. Iron overload and HCV infection are independent risk factors for liver fibrosis progression, and their concomitant presence results in a striking increase in risk [71]. Insulin resistance, steatosis and/or obesity are now recognized as important risk factors for fibrosis progression [56,72]. Diabetes and steatosis induced by steroids and parenteral nutrition after HCT may explain this observation. In the immediate post-transplant period, the donor response is limited because of immunosuppressive treatment. The HCV replication rate exceeds largely the kinetics of the immune response such that the effector-to-target cell ratio favours the virus. The HCV virus load is upper the observed level in HCV-infected non-transplanted patients (data not shown). The virus extension is rapid to a high number of hepatocytes. NK compartment is the first to recover after transplant [73]. It has recently been shown that high concentration of recombinant HCV N2 inhibits their cytotoxicity and cytokine production [74,75], as it could be the case after HCT. Regulatory T cells are able to protect mice from GVHD [76]. Their potential role is still discussed in humans [77]. It was recently shown that a high proportion of the cellular infiltrate in persistent HCV infection includes FOXP3-positive cells [78]. We can hypothesize that Regulatory T cells are able to inhibit the immune response after HCT and favour chronic liver disease. Specific humoral immune response takes time and is limited after HCT [73]. Reconstitution of the immune system after a period of depressed cellular immune responses increases inflammatory activity in the liver, with enhanced HCV-specific immune responses [27]. Moreover, in chronic HCV patients, ALT elevation is more frequent, severe and protracted following HCT compared to autologous

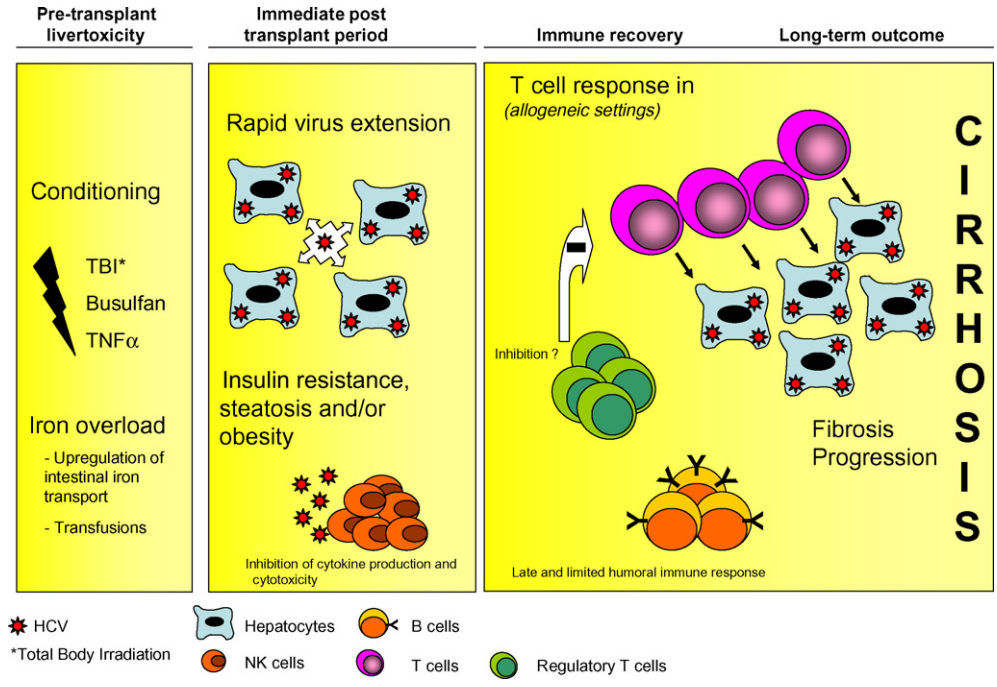

Fig. 2. Physiopathology of liver lesions in Stem cell transplant recipients with chronic hepatitis C. There are specific factors due to the allogeneic and immunosuppressed context that are responsible for quicker fibrosis progression: *Pre-transplant liver toxicity:* the conditioning may directly support the liver injury, as well as inflammatory cytokines. Iron overload (transfusions) is also responsible for liver fibrosis. *Immediate post-transplant period:* the HCV replication rate exceeds largely the kinetics of the immune response. The virus extension is rapid to a high number of hepatocytes. Insulino resistance, steatosis and/or obesity are now recognized as important risk for fibrosis progression. *Immune recovery:* NK compartment is the first to recover after transplant. HCV is able to inhibit NK cell cytotoxicity and cytokine production. Specific humoral immune response takes time and is limited after HCT. Reconstitution of the immune system after a period of depressed cellular immune responses increases inflammatory activity in the liver, with enhanced HCV-specific immune responses. *Long-term outcome:* a more rapid rate of liver fibrosis progression is observed in HCV-infected HCT patients with an expected median time to cirrhosis of about 18 years after HCT.

transplantation [79]. The allogeneic presentation may enhance the immune response. Many unanswered questions thus remain in the context of HCT and there is a need for large prospective studies on this specific population to elucidate the different steps for fibrosis progression.

6. Treatment

6.1. HCV therapy in non-transplanted HCV-infected patients

The primary aim of treatment is viral eradication, resulting in cure of infection [80–83]. The other aim is to prevent, stabilize, or obtain regression of fibrosis. To date, in a patient with HCV, combined therapy associating pegylated alpha interferon and ribavirin results in a sustained virological response in approximately 55% of cases [84,85]. In these two studies, the sustained virological response was approximately 80% in genotype 2 or 3 infection a with 24-week treatment duration and 50% in genotype 1 with a 48-week duration. Based on existing results, the sustained virological response with this treatment option appears to be long-lasting, to be associated with a histological benefit and is also probably associated with a reduction in the risk of cirrhosis and hepatocellular carcinoma. The pre-therapeutic predictive factors of efficacy of treatment are mainly linked to the virus (genotype non-1 and low viral load) and less to the patient (female sex, younger age, less severe liver disease, minimal or moderate fibrosis) [84,85].

6.2. HCV therapy HCV-infected HCT patients

Unfortunately, little has been published specifically concerning the treatment of HCV-infected SCT recipients. During the transplant period, RBV has been used to prevent immediate liver disease by HCV [86]. However, only one study reported the effects of standard IFN therapy in SCT recipients with only 10 patients completing the protocol, of whom five responded to treatment [87]. Four of these five patients had persistently undetectable HCV-RNA. We recently described our experience in the treatment of these patients. We were able to treat only 22 of 36 SCT recipients who needed anti-HCV therapy because of liver disease (moderate to advanced fibrosis) but who also had treatment contraindications. We obtained a sustained virological response in 6 out of 22 patients (27%), 4 of whom were treated with combination therapy. Although only a few patients were treated, the combination treatment seemed more effective in achieving sustained virological response. However, the combination therapy also resulted in more hematological complications. While anemia could be easily managed with dose modification and/or erythropoietin, thrombocytopenia mostly led to treatment interruption [88]. It is noteworthy that no IFN treatments induced or precipitated GVHD.

Those results are in accordance with what is observed in other immunocompromised individuals. HCV treatment is thus often associated with a poor response. Among 106 patients co-infected with HIV/HCV, only 16% had a sustained virological response mainly because of discontinuation due to adverse events [89]. In liver transplantation, PEG IFN and RBV treatments achieved virological response in 9 out of 20 patients (45%). Treatment was withdrawn in four patients (20%) and the dose of PEG IFN and of RBV was reduced for six and 13 patients, respectively [90]. These results have been confirmed recently [91].

In clinical practice, liver biopsy should be performed to evaluate precisely the severity of liver disease (fibrosis, necroinflammantion), determine its prognosis and direct the choice of the therapeutic options. Combination therapy with pegylated interferon and ribavirin could be recommended for this particular population, in patients with moderate to advanced fibrosis. The literature emphasizes the difficulty in obtaining a sustained virological response in such patients, mainly because of treatment discontinuation due to adverse events, and also partly because of difficulty in attaining a strong immune response [92]. Treatment efficacy seems to increase if treatment is begun at an optimal dose with close follow-up so that the doses can be rapidly modified to avoid stopping treatment. Good compliance to treatment is essential. Potential psychological disturbances should be anticipated (depression). Undesirable side effects that might require lowering doses should be rapidly identified. In our experience, the use of growth factors and erythropoietin enabled continuation of the treatment in some cases. New drugs, such as viral enzyme inhibitors (proteases and polymerases), are expected to improve the efficacy of HCV therapy in the near future [93–95].

6.3. Guidelines in the context of HCT

Concerning the donor, in case of HCV infection, an alternate donor should be considered if available. If there is no other donor, HCT is not contraindicated because of HCV infection. First, a specific treatment of the donor is possible before marrow or stem cell harvest allowing a HCV-negative sampling [96,97]. Second, acquiring HCV during transplant from an HLA-matched but HCV-infected donor is associated with low morbidity in the subsequent 10 years compared to a less well matched HCV-negative donor. Third, we have to keep in mind the major risk of relapse in case of hematological disease and that most of the time it will not allow HCV treatment of the donor before HCT.

In case of HCV infection diagnosed before transplant, active liver disease or cirrhosis should be assessed by biopsy. It is recommended to treat the patient before the stem cell infusion in view of the risk of the hematological disease. At the time of transplant, prevention of sinusoidal injury is fundamental in case of advance chronic liver disease, portal hypertension or cirrhosis. The actual recommendation is to use a sinusoidal toxin-free regimen, such as non-myeloablative conditioning [44], if such a regimen is not worse in terms of anti-tumor activity and, of course, if the patient does not present any other co-morbidity [98]. After transplant, patients should be evaluated for the development of chronic hepatitis (clinic and liver biopsy), and also because of the unusual hepatic variant GVHD presentation that needs urgent treatment. The patients who showed fibrosis progression should be treated if they do not have on-going chronic GVHD and/or an intensive immunosuppressive therapy.

7. Conclusion

While the risk of acquiring HCV infection is now extremely low, it is not uncommon for patients to come to HCT already infected. Pre-existing HCV infection seems to be associated with an increased risk of severe SOS [5,99,100] but the immediate post-transplant period is rarely a problem. The long-term follow-up has been recently shown to be associated with an increased risk of earlier cirrhosis compared with HCV-infected non-transplanted patients. The rate of fibrosis progression is higher in HCV-infected HCT recipients than in the non-transplanted control group, which is in accordance with what is observed in other immunocompromised patients [59–63]. Histological liver evaluation should be performed in all patients after HCT to evaluate the stage of fibrosis and grade of necroinflammation. In candidates for HCV therapy, patients may benefit from combined PEG IFN and RBV treatment in the absence of chronic GVHD and/or an intensive immunosuppressive therapy. This treatment clearly needs close clinical and biological monitoring to prevent side effects in this particular population.

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