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## Hepatitis C virus and allogeneic stem cell transplantation still matters!

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Allogeneic Hematopoietic Cell Transplantation (HCT) is widely used to cure patients with hematologic disorders. Nearly 90% of the patients who survived free of their original disease more than two 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 sinusoidal obstruction syndrome (SOS; formerly known as veno-occlusive disease), Graft-versus-Host Disease (GvHD), drug toxicity, post-transplantation viral hepatitis and disease relapse. Among long-term survivors, cirrhosis is an important late complication of HCT.[2,3]

The hepatitis C virus (HCV), identified in 1989, is an enveloped RNA-virus with a 9.6kb single strand genome. A significant proportion of long-term HCV-infected HCT survivors, primarily contaminated through blood exposure, develop cirrhosis and hepatocellular carcinoma during the long-term follow-up.[4,5] Moreover, HCT recipients showed a higher rate of liver fibrosis progression as compared with HCV-infected patients who did not receive a transplant.[5] HCV-related disorders and the prognostic implications of hepatitis C seropositivity after allogeneic HCT will be shortly summarized here, more detailed reviews can be found in recent publications.[2,3] 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 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 ten years ago, rarely accounts for recently acquired infections owing to systematic screening of blood products for HCV.[2,3]

### Hepatitis C in allogeneic hematopoietic cell transplant donors

It may turn out that the only available donor is HCV antibody and RNA positive. Regulatory issues may then arise in some countries knowing that HCV will usually be transmitted, and that the rate of spontaneous viral clearance is likely to be low. Treatment of the donor with pegylated interferon plus ribavirin prior to harvest of donor cells may render them non-viremic and much less likely to transmit infection. If the virus is transmitted, the acute phase of HCV infection may cause elevated liver enzymes at 2–3 months post HCT, after recovery of T-cell function; however, severe hepatitis is rare, and the outcome in ten years of follow-up is no different than in transplant recipients without hepatitis C infection.[6] In the long-term, treatment should be offered to the recipient who remains with active hepatitis as such a patient is at risk for development of cirrhosis and hepatocellular carcinoma.

### Chronic hepatitis C in candidates for hematopoietic cell transplant

Patients with active liver disease, particularly those with severe hepatic fibrosis or cirrhosis, are at increased risk for fatal sinusoidal obstruction syndrome (SOS) following some myeloablative regimens, (notably regimens that contain cyclophosphamide or total body irradiation over 12 Gy), and the presence of cirrhosis may provide a contraindication to any high-dose conditioning regimen. Patients with cirrhosis are at risk for fatal hepatic decompensation after HCT even if given a reduced-intensity conditioning regimen.[7] Liver biopsy should be considered before the start of conditioning therapy if there is a clinical suspicion of cirrhosis or extensive fibrosis resulting from chronic viral infection.

### Prognostic implications of hepatitis C virus infection after allogeneic hematopoietic cell transplant

#### *Short-term outcome*

In the first three months after transplant, liver dysfunctions related to HCV are usually mild[6,8-10] limited to

a five to ten-fold increase in alanine aminotransferase (ALT).[8] Several causes of liver dysfunctions are present at this time. The main problem during this period is to differentiate between acute GVHD and viral hepatitis. Unless there is evidence of active GVHD in other organs, a liver biopsy is usually needed before a therapeutic decision is made. Pathological 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, loss of interlobular bile ducts, and cholestasis in zone 3 of the liver acinus are more typical of GVHD.[4,6,11,12] After three months, the occurrence of late viral hepatitis is possible, which coincides with a decrease in or discontinuation of immunosuppressive therapy and a return of cellular immunity.[2,3] The most difficult situation at this time is the unusual presentation of liver GVHD (hepatic variant), resembling viral hepatitis,[7,13] in which liver biopsy is essential to confirm GVHD.

In literature the potential role of HCV in the development of SOS was for a long time a matter of debate .[2,3] A 9.6-fold increased risk of fatal SOS was demonstrated in HCV-infected patients who received cyclophosphamide and TBI over 12 Gray, related to sinusoidal toxins of those regimens and not directly to HCV.[6] In other words, the increased risk of a fatal outcome from sinusoidal toxicity is related to fibro-inflammatory liver disease and the components of the conditioning regimen, and not to HCV per se. HCV infection is not considered as a risk factor for SOS if the conditioning regimen has little or no liver toxicity, for example, fludarabine and targeted busulfan or a non-myeloablative regimen of fludarabine plus low-dose TBI.[7]

In this issue of the journal, Ramos and co-workers report a case-control study of the outcomes of 31 patients who were HCV seropositive at the time of allogeneic HCT.[14] HCV patients were considered candidates for stem cell transplantation only if they had no significant evidence of hepatic dysfunction. Matched controls (n = 31) were seronegative for viral hepatitis and were paired on age, diagnosis, disease stage, conditioning regimen and donor type. Authors also compared the HCV patients to all seronegative patients (all controls, n = 1,800) transplanted during the same period, to adjust for other confounding effects. The median age of the HCV patients was 49 years, all were transplanted for hematologic malignancies, 61% had poor risk disease, most had related donors and were transplanted after a reduced intensity conditioning, 7 patients had abnormal alanine transaminase levels less than 3 times the upper limit of normal and one patient elevated bilirubin. These characteristics were similar to those of the matched control group. Median overall survival was three, 18 and 20 months, and one year survival was 29%, 56% and 56% in the HCV, matched and all controls groups respectively (hazard ratio for death 3.1, $p<0.001$ in multivariate analysis). Non-relapse mortality at one year was 43%, 24% and 23% respectively (HR 3.3, $p<0.01$). Disease progression and GVHD rates were comparable. Thus, HCV seropositivity remained a significant risk factor for non-relapse mortality after allogeneic hematopoietic stem cell transplantation even with normal or minimally abnormal liver function tests. Two points should be underlined in this study: first, while disease recurrence and GvHD were leading causes of death both in patients and controls, 3 deaths in HCV-infected individuals (non-SOS-related liver failure, multi-organ failure and hemorrhage) could potentially be related to HCV liver disease; second, 4 deaths in HCV-infected patients (17%), and one death in the control group, were infectious. Although limited from a statistical point of view, it should be stressed that in our experience on the long-term follow-up of HCV-infected patients we have already reported an excess of late bacterial infection, thus raising the question of HCV-linked immune deficiency.[5]

*Long-term outcome (Table 1)*

For a long time, HCV infection was not considered a major problem after HCT. The first study which directly assessed the impact of HCV infection in long-term survivors after HCT was conducted by Ljungman *et al.* in 1995. The diagnosis was based on the HCV positivity either by PCR for HCV RNA or by second generation tests. 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, with a median follow-up time of six years.[8] Thomas *et al.* with a similar follow-up also did not found evidence of cirrhosis.[17] In 1999, the Seattle

**Table 1.** Retrospective analysis of hepatitis C virus infection in the long-term follow-up after hematopoietic cell transplantation.

| Sources | Year | N. of HCV patients | HCV diagnosis | Median follow-up (years) | HCV related complications |
|---|---|---|---|---|---|
| Locasciulli *et al.*[15] | 1991 | 38/128 | Serology | 2 | Hepatitis exacerbation after HCT<br>More severe liver damage (biopsy) in anti-HCV+ patients |
| Norol *et al.*[16] | 1994 | 14/120 | Serology | Not given | More chronic liver disease in HCV+ patients |
| Ljungman *et al.*[8] | 1995 | 28/161 | Serology and PCR | 6.1 | No difference according to HCV status |
| Strasser *et al.*[6] | 1999 | 113/355 | PCR | 10.4 | No difference according to HCV status |
| Thomas *et al.*[17] | 2000 | 29/61 | Serology and PCR | 6 | No increase of morbidity or mortality |
| Peffault de Latour *et al.*[5] | 2004 | 96/686 | PCR | 15.7 | 15 patients with biopsy proven cirrhosis |
| Ivantes *et al.*[18] | 2004 | 31/80 | Serology and PCR | Patients studied were alive at least ten years after HCT | 3 cirrhosis within the 22 HCV patients studied |

group reported a cohort of 355 patients from which 113 (32%) were HCV RNA positive. During a ten year 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.[6] 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 ten years. Among 3,721 patients who survived one or more years after HCT, 31 developed cirrhosis. Cirrhosis was attributed to HCV in 15 of 16 patients presenting more than ten years after HCT.[4] In our experience, 15/96 patients, HCV-infected recipients developed biopsy-proven cirrhosis at a median follow-up of 15.7 years with 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 ten years after transplantation in 13 of our 15 patients. We thus observed 3 hepatocellular carcinoma.[5] Ivantes *et al.* also found cirrhosis in a smaller group of patients followed more than ten years after HCT.[18] Thus, HCT recipients with HCV infection present a high risk of cirrhosis, and data from the Paris group also suggest that HCT-recipients develop fibrosis sooner than non-transplanted HCV-infected individuals.

### *Treatment*

Little has been published specifically concerning the treatment of HCV-infected HCT recipients. During the transplant period, ribavirin has been used to prevent immediate liver disease by HCV.[19] However, only one study reported the effects of standard IFN therapy in SCT recipients with only 10 patients completing the protocol, of whom 5 responded to treatment.[20] Four of these 5 patients had persistently undetectable HCV RNA. We described our experience and reported that we were able to treat only 22 of 36 HCT recipients who needed anti-HCV therapy because of liver disease (moderate to advanced fibrosis). We obtained a sustained virological response in 6 out of 22 patients (27%), among whom 4 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 hematologic complications. While anemia could be easily managed with dose modification and/or erythropoietin, thrombocytopenia mostly led to treatment interruption.[21] There is no published experience with newer antiviral approaches (protease and polymerase inhibitors) to HCV infection in transplant survivors.

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