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Long-term follow-up of HCV infected hematopoietic stem cell transplant patients and effects of antiviral therapy

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Abstract

This prospective study was initiated in 1993 with the aim to study late effects and responses to antiviral therapy in a cohort of HCV infected patients. 195 patients were included from 12 centers. 134 patients had undergone allogeneic and 61 autologous HSCT. The median follow-up from HSCT is currently 16.8 years and the maximum 27.2 years. 33 of 195 patients have died of which six died from liver complications. The survival probability was 81.6% and the cumulative incidence for death in liver complications was 6.1% at 20 years after HSCT. The cumulative incidence of severe liver complications (death from liver failure, cirrhosis, liver transplantation) was 11.7% at 20 years after HSCT. 85 patients have been treated with interferon; 42 in combination with ribavirin. The sustained response rate was 40%. The rates of severe side effects were comparable to other patient populations and no patient developed significant exacerbations of GVHD. Patients receiving antiviral therapy had a trend towards a decreased risk of severe liver complications (OR 0.33; p=.058). HCV infection is associated with morbidity and mortality in long-term survivors after HSCT. Antiviral therapy can be given safely and might reduce the risk for severe complications.

Keywords: Hepatitis C virus; antiviral therapy; late effects

Introduction

An increasing number of patients having undergone hematopoietic stem cell transplantation (HSCT) become long-term survivors. Late-effects have thereby become of major interest influencing survival and quality of life. Chronic Hepatitis C virus (HCV) infection has been suggested to be an important cause of morbidity and late mortality after HSCT. HCV is transmitted primarily through exposure to blood from infected individuals and is a major cause of liver disease in the world and the most common chronic blood-borne infection in the United States. Although the number of new infections has declined by more than 80% since the 1990s due mainly to better strategies to prevent blood transmission of HCV up to 40% of chronic liver diseases are HCV related. Published studies suggest that the long-term impact of HCV in HSCT patients is significant with a proportion of patients going into liver failure or developing hepatocellular carcinoma [1-4]. Peffault de Latour et al reported data from a retrospective evaluation of 96 patients infected by HCV with a median follow-up 15.7 years. The cumulative incidences of biopsy proven cirrhosis at 15 years and 20 years were 11% and 24%, respectively [3]. The impact of therapy on long-term outcome of HCV infection in HSCT recipients is mainly unknown as is the risk for side effects of interferon based antiviral therapies. In 1993, the Infectious Diseases Working Party of the European Group or Blood and Marrow Transplantation (EBMT) launched a prospective study with the aim to follow a cohort of HCV infected patients over time. The aims of the study were to determine the long-term outcome, to estimate the liver associated morbidity and mortality, and to assess the response to antiviral therapy.

Patients and Methods

In 1993, all EBMT member centers were asked regarding participation in the study. The requirements for the center to participate were to be willing and able to report baseline data on all

HCV infected allogeneic or autologous HSCT patients having survived for at least 6 months and to send follow-up reports approximately every five years. The ethical committee at Karolinska Institutet, Stockholm, Sweden approved the study. Additional ethics approval has been obtained at the local participating centers as required. The EBMT rules require that patients reported to the EBMT registry should give consent to data registration.

Data collection: Investigators from 17 transplant centers accepted participation and included a total of 236 patients into the study between 1993 and 1996. A questionnaire was sent to collect the baseline data. After the study start, three additional data request forms have been sent to the centers in 1997, 2003 and in November 2007. No follow-up report was received on 41 patients and these were regarded as lost to follow-up leaving 195 patients (82.6%) of the original cohort to be analyzed. In order not to overestimate survival due to lack of follow-up, the EBMT registry megafile was used to update survival and collect the cause of death as available. The EBMT megafile was also used to verify the baseline patient data.

Diagnosis of HCV infection: Diagnosis of HCV infection was made by serological testing (RIBA), PCR, or both. Genotyping of HCV has been performed according to the centers local routines and reported if available.

Follow-up and antiviral therapy: Patients were followed according to each participating center's normal routines and no protocol specific sampling or diagnostic procedure was performed. Antiviral therapy was given according to each center's routines and varied over time. Chronic GVHD was scored as reported by the investigators and biopsy confirmation was not required.

Statistics

Kaplan-Meier curves were calculated for overall survival. Cumulative incidences were calculated for death from liver failure with death from other causes as the competing risk and for development of severe liver complications including death from liver failure, liver transplantation, and biopsy verified cirrhosis with death occurring without the diagnosis of severe liver complication as the competing event. Uni- and multivariable logistic regression was performed with the aim to determine risk factors for severe liver complications.

Results

Of the analyzed cohort, 134 patients had undergone allogeneic and 61 autologous HSCT. Patient characteristics for the two cohorts are shown in table 1. The median time from SCT to inclusion into the study was 4.5 years (0.5-21.5). The median follow-up from SCT is 16.8 years and the maximum follow-up is 27.2 years.

HCV infection:

67 patients were diagnosed by RIBA and 128 patients by PCR or by RIBA subsequently complemented by PCR. Twelve patients (6%) were seropositive by RIBA but PCR negative while nine patients were PCR positive but RIBA negative. Genotype information exists for 80 patients; 63 patients had type 1 (1a = 12; 1b = 41), 12 had type 2 (2a = 1; 2b = 7; not subtyped = 4), and five patients type 3 (3a = 3; not subtyped = 2). It is not possible to determine when the patients became HCV infected since the patients might have been infected before or after HSCT and the HCV was documented first after HSCT in most patients. However, the median time from diagnosis of HCV infection to last follow-up was 14.5 years.

Survival: 33 of 195 patients have died. The main causes of death were the original hematological disease in 11 patients, secondary tumors (no liver carcinoma documented) in seven, liver failure or death after liver transplantation in six, other infections in five, other causes in two, and in two patients the cause of death was unknown. The Kaplan-Meier probabilities of survival were 83.9 % and 81.6% at 15 and 20 years after HSCT, respectively (figure 1). The corresponding probabilities for allogeneic HSCT recipients were 88.1% and 87.1% and in autologous HSCT recipients 73.8% and 67.9% at 15 and 20 years after HSCT, respectively.

Liver complications: Four patients died from liver failure (one patient from combination of HCV and alcohol abuse, one from hepatic coma while details for the other two are not given) and two died following liver transplantation. Three of 134 allogeneic and 3 of 61 autologous recipients. The cumulative incidence for dying from hepatic causes were 4.1% at 15 years and 6.1% at 20 years after HSCT (3.3% and 5.8% in allogeneic and 6.4% in autologous recipients at both 15 and 20 years after HSCT, respectively; figure 2).

120/195 patients had at least one liver biopsy performed during follow-up. Nine patients are alive with documented liver cirrhosis, two additional patients have undergone liver transplantation and are currently alive, and two patients died from other causes (original disease and infection) but had documented liver cirrhosis. The cumulative incidence of severe liver complications (death from liver failure, liver transplantation, living with cirrhosis, died from other cause with established cirrhosis) was 6.9% at 15 years and 11.7% at 20 years (5.6% and 11.2% in allogeneic and 8.3% at 15 and 13.7% at 20 years in autologous HSCT recipients). There was no correlation between chronic GVHD and severe liver complications; 3/59 (5.0%) with and 8/75 (10.7%) allogeneic HSCT recipients without chronic GVHD developed severe liver complications. There was also no

difference in risk for severe liver complications between patients who had HCV diagnosed by serology or PCR (=.30). Two patients are reported to have cryoglobulinemia presumed to be associated with HCV infection.

Therapy for HCV infection: Overall 85/195 patients have been treated with interferon based therapy with or without the addition of ribavirin. 14 patients have been treated more than once usually with interferon given alone as the first course of therapy and with the combination of interferon and ribavirin as the subsequent therapy. Thus, a total of 99 courses of antiviral therapy were administered (47 courses of interferon given as single therapy, 38 courses of interferon in combination with ribavirin, and 14 courses with the combination of pegylated interferon and ribavirin. The median time from HSCT to first course of therapy was 9.3 years. At the last follow-up report, 41 patients had become PCR negative of whom seven had relapsed, 25 did not respond, three were not yet evaluated, and for 16 the PCR status was unknown. The responses split by HCV genotype were: 11 patients became PCR negative of 32 treated for genotype 1, five of eight for genotype 2, and two of three for genotype 3. The sustained response rates for interferon given as a single drug were 31% (10/32) with data missing for seven patients, 57% (16/28) for interferon in combination with ribavirin with data missing for 2 patients, and 67% (6/9) for pegylated interferon in combination with ribavirin with data missing for 6 patients three of these not yet evaluated. The sustained response rates were significantly higher for the combinations with ribavirin compared to interferon alone (p=.02). In addition two patients were treated with ribavirin alone and were PCR negative at last follow-up [5]

Side effects from therapy: The centers were asked to report severe side effects of therapy. In 51 of 85 patients, no severe side effect was reported. The most common significant side effects were

similar to what is seen in other patient populations (anemia, asthenia, musculo-skeletal pains, and hair loss). Five patients were reported to have developed leucopenia and/or thrombocytopenia. Two patients required blood transfusions. Significantly increased GVHD activity was not reported in any patient.

Other therapies: 55 patients were given treatment to decrease iron overload in most cases by venesectio. 126 patients had no received such treatment while there was no information in 14 patients.

Risk factors for developing severe liver complications: In a multivariable logistic regression age at HSCT (p=.03; OR 1.04; 95% CI 1.01-1.08) was the only significant factor while antiviral treatment showed a strong trend to reduce the risk for severe liver complications (OR 0.33; 95% CI .11-1.03; p=.058). In a model only including allogeneic HSCT recipients, there was no effect on the risk by age or the presence or absence of chronic GVHD while antiviral therapy was again borderline significant (p=.066).

Discussion

Hepatitis C virus was discovered in 1989 and it was early recognized that patients with hematological diseases were highly likely to have become infected if they had received multiple blood transfusions before the diagnostic procedures with serological assays and later with PCR were introduced into routine clinical practice in the blood banks during the early 1990-ies. Many HCV infected patients therefore underwent HSCT and the infection either was detected after the transplantation when the diagnostic procedures became available or patients underwent HSCT with a known infection. A couple of long-term follow-up studies analyzing retrospectively the

outcome of HCV infected patients have been published [3, 4]. Our study differs from the previously published studies by being prospective including a cohort of patients registered into the study between 1993 and 1996 and followed for 15 years. In addition the study is significantly larger than the previously published studies both regarding the number of patients included and in the number of patients receiving antiviral therapy against HCV.

We chose to exclude patients dying the first 6 months after HSCT to concentrate on late complications and to include patients transplanted long time before the diagnostic techniques for HCV became available. Thus, we cannot be certain if the patients were infected before or after transplant but on the other hand it extended the time from infection to last follow-up.
In our study cohort, the current survival probabilities were 83.6% at 15 years and 81.6% at 20 years after HSCT. This overall survival probability seems high compared to other studies reporting long-term survival data but it should be noted that the median time from HSCT to inclusion in our study was 4.5 years thereby excluding many of the early common causes of death after HSCT including acute GVHD, early infections, and relapse from the original disease. Pre-transplant HCV infection has, in some but not all studies, been associated with an increased risk for VOD and these events would most likely be excluded by our design excluding patients dying the first 6 months after HSCT [6-9]. Furthermore, in a recent study, seropositivity to HCV was reported to confer an increased risk for non-relapse mortality during the first year after HSCT [10]. Although we chose to use the time from HSCT for calculating survival since that is the meaningful information for clinicians following patients, the results are similar using a landmark analysis from time of registration into the study (data not shown).

Liver disease was directly implicated as a cause of death in 6/195 patients resulting in a cumulative incidence of 4.1% at 15 years after HSCT This figure is lower than what found by Peffault de Latour et al although a cumulative incidence was not reported in their paper [3]. In their study 8/95 patients died from end stage liver disease suggesting at least a double risk compared to what was found in our study. One difference between the studies is that our study included patients undergoing both allogeneic and autologous HSCT, but in fact we found a tendency to a lower risk for dying from liver disease in the allogeneic HSCT recipients so that is unlikely to be the explanation. Another difference between the studies is that Peffault de Latour et al documented three deaths from hepatocellular carcinoma while no patient in our cohort so far has developed this complication, despite the median survival in the two studies being similar.

In our study cohort, the cumulative incidences of severe liver complications were 6.9% at 15 years and 11.7% at 20 years. These figures are also lower than those found by Peffault de Latour et al who reported incidences of cirrhosis at 15 and 20 years of 11% and 24%, respectively [3]. One third of our patients were primarily diagnosed by serology and not by PCR and this could have influenced the results but there was no significant difference in the risk for liver complication between the groups diagnosed by serology or PCR. The proportions of patients who had liver biopsies were similar in both studies (61.5% in our study and 69.7% in the study by Peffault de Latour et al). In another small single center study, 13.6% were reported to have liver cirrhosis [4]. The reported annual progression rate to severe complications in a large, retrospective study of HCV infected individuals was 0.8% in patients who did receive antiviral therapy and 3.7% in patients without such therapy [11]. In an epidemiological review of patients with HCV, the reviewed information reported that 20% of patients would develop liver cirrhosis over a period of 20-25 years [12] suggesting that our rate of 11.7% at 20 years after HSCT, and probably in many patients

longer time since infection, does not represent a substantial difference compared to other non-transplanted HCV-infected populations.

There are different possibilities explaining our lower risk for severe liver disease than what was found in the study by Peffault de Latour et al [3]. One reason could be the prospective design of our study although it should be recognized that follow-up many years after HSCT is likely to be with long intervals and also the risk for patients being lost to follow-up increases over time. Six percent of the patients were also PCR negative at inclusion into the study. Since there were no prespecified procedures for diagnosis of liver complications at the participating centers, mild cases of cirrhosis can of course have been missed. Another possibility is the positive impact of antiviral therapy. In a separate paper, the same group from Paris reported data on 22 patients who had received antiviral therapy [13].This study is until now the largest reporting the outcome of antiviral therapy in HCV infected HSCT recipients. In our cohort, 85 patients (45.6%) have until now received interferon based antiviral therapy with a response rate of 50% assessed as becoming PCR negative. Furthermore, we found that antiviral strongly reduced the risk for the development of severe liver complications with two thirds (OR 0.33; p=.058). Therapy could also be given safely since the number of serious side effects was quite low and the types what could be expected in an otherwise healthy population. In addition, there were no signs indicating a risk for worsened chronic GVHD in patients having undergone allogeneic HSCT. Therefore the benefit vs. risk ratio is clearly in favor for giving antiviral therapy to HCV infection HSCT recipients.

Peffault de Latour et al found an increased risk for development of cirrhosis in patients with HCV subtype 3 [3]. We were unable to verify this finding but unfortunately less than half of our study population had HCV genotyping performed and among those with known subtypes, very few

patients had subtype 3. In our study, we found a significant impact on the risk for severe late liver complications by age at transplantation. In other patients cohorts age is a factor correlated to progression together with alcohol abuse, co-infection with HBV or HIV, immunosuppression, and iron overload (in thalassemia patients) [11, 14-17]. We also found age being an independent risk factor for progression to serious liver disease. In our cohort, approximately 30% have been treated to reduce the iron load. Immunosuppression did not seem to have any long term negative effects on outcome since we found no higher risk for development of cirrhosis in patients having received an allogeneic HSCT. In liver transplant patients, risk factors for progression were increased liver function tests, high viral load, and steroid pulse therapy given for rejection [18]. All patients in our study were of course immunosuppressed at some stage but we were unable to show an increased risk for severe liver complications in allogeneic patients with chronic GVHD suggesting that receiving prolonged immunosuppressive therapy had no influence on the risk for severe liver complications.

The data suggest that the response and relapse rates of HCV infection after antiviral therapy in our patient cohort are similar to what can be found in other patient groups and higher than what was found by Peffault de Latour et al [13]. It should, however be noted that PCR follow-up data is lacking on 20% of the patients but if we only look at the patients for whom data are known, 34/56 (61%) had sustained virological responses and even if all patients without follow-up are counted as failures (which is an unlikely scenario), the sustained response rate was 40% compared to 20% in the study by Peffault de Latour et al [13] and similar to what was found in a recent study of non-HSCT patients [19]. More importantly, the therapy seemed to be safe with frequencies and types of significant side effects similar to what can be found in other patient populations and no patient was reported to need discontinuation of antiviral therapy due to an exacerbation of chronic GVHD.

In summary, HCV infection is associated with morbidity and mortality in long-term survivors after HSCT. Liver biopsies should be performed to assess the degree of liver damage in infected patients. Antiviral therapy might reduce the risk for severe liver complications and can be given safely with similar rates of side effects and antiviral response as in non-HSCT patients.

Authorships and disclosures

PL: study concept and methodology, data acquisition and interpretation, statistical analysis, and manuscript writing; AL: study concept and methodology, data collection, and commented on the manuscript; VGGS, AB, LB, IE, AF, IF, MR, PS: data collection, and commented on the manuscript; JOR, HE: study concept and methodology, data collection, and commented on the manuscript. All authors approved the final version of the manuscript.

None of the authors have any potential conflicts of interest regarding this study.

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Table 1. Patient characteristics

Characteristic		Allogeneic HSCT patients	Autologous HSCT patients
		N = 134	N = 61
Median age		20.9 (0.4-52.3)	30.2 (3.1-58.1)
Gender (M/F)		78/56	35/26
Diagnosis			
AML	CR1	38	34
	More advanced disease	8	5
ALL	CR1	19	8
	CR2	11	4
	More advanced disease	5	0
Aplastic anemia		17	0
CML	CP1	17	2
	More advanced disease	2	0
Lymphoma		2	7
Myeloma		1	1
MDS		5	0
Thalassemia		7	0
CLL		1	0
Inborn error		1	0
Donor type			
HLA identical sibling		129	NA
Other family		2	NA
Unrelated		2	NA
Syngeneic		1	NA
Stem cell source			
Bone marrow		134	52
PBSC		0	9
Chronic GVHD			
Limited		15	NA
Extensive		34	NA

Figure legends

Figure 1: Overall survival from transplantation for HCV infected allogeneic and autologous patients.

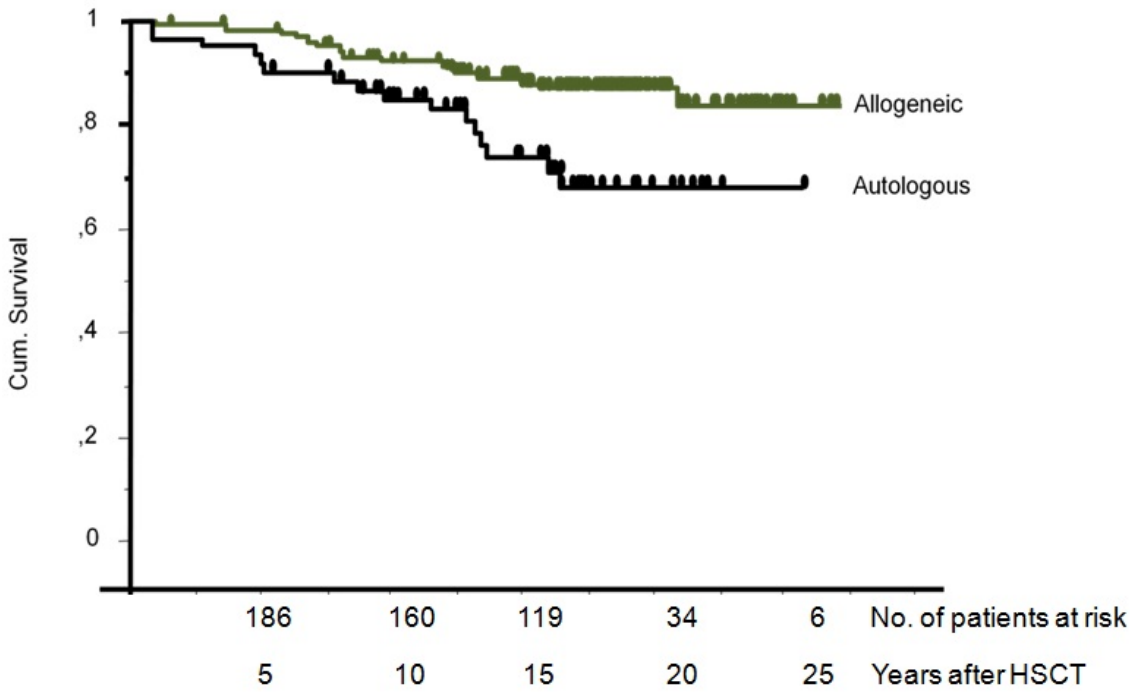
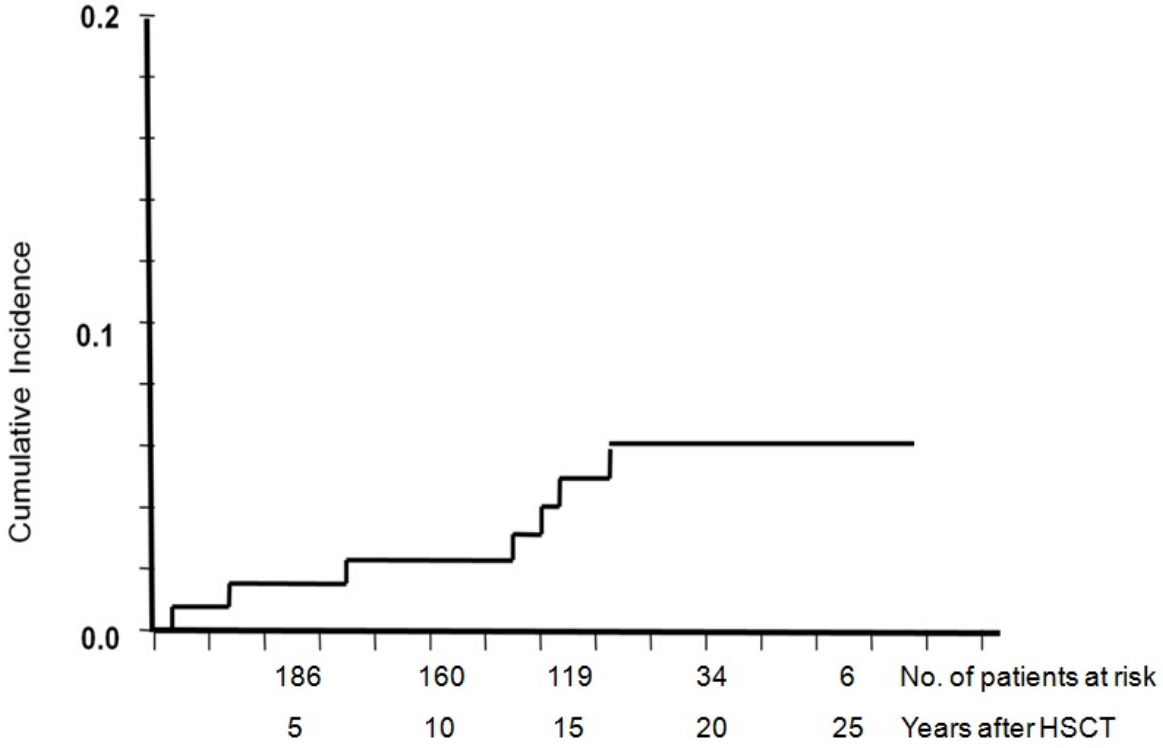
Figure 2: Cumulative incidence of death from liver complications for HCV infected patients..