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RESULTS OF LIVER TRANSPLANTATION IN THE DEPARTMENT OF GENERAL, TRANSPLANT AND LIVER SURGERY AT THE MEDICAL UNIVERSITY OF WARSAW IN PATIENTS WITH CHRONIC HEPATITIS B AND C VIRUSES INFECTION

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ABSTRACT

INTRODUCTION. Cirrhosis related to hepatitis C virus (HCV) and hepatitis B virus (HBV) infection is the most frequent indication for liver transplantation worldwide. Progress in prophylaxis of posttransplant HBV recurrence has led to major improvements in long-term outcomes of patients after liver transplantation. Conversely, impaired posttransplant survival of patients with HCV infection was reported in several studies, mainly due to recurrence of viral infection. The purpose of this study was to compare long-term results of liver transplantation between patients with HBV monoinfection, HCV monoinfection and HBV/HCV coinfection.

MATERIAL AND METHODS. A total of 1090 liver transplantations were performed in the Department of General, Transplant and Liver Surgery in cooperation with the Department of Immunology, Internal Medicine, and Transplantology at the Transplantation Institute Medical University of Warsaw between December 1994 and May 2012. After exclusion of patients with cirrhosis of non-viral etiology, patients with malignant tumors, and patients with acute liver failure, the final study cohort comprised 209 patients with HBV (HBV+/HCV- subgroup; n=56) or HCV (HBV-/HCV+ subgroup; n=119) monoinfection or HBV/HCV coinfection (HBV+/HCV+; n=34). These subgroups of patients were compared in terms of long-term results of transplantations, defined by 5-year patient and 5-year graft survival estimates.

RESULTS. Overall and graft survival rates after 5-years for the whole study cohort were 74.5% and 72.6%, respectively. Five-year overall survival was 70.4% for patients within the HBV+/HCV- subgroup, 77.8% for patients within the HBV-/HCV+ subgroup, and 68.5% for patients within the HBV+/HCV+ subgroup. The corresponding rates of graft survival were 67.0%, 76.3%, and 68.5% for patients within the HBV+/HCV-, HBV-/HCV+, and HBV+/HCV+ subgroups, respectively. Observed differences were non-significant, both in terms of overall (p=0,472) and graft (p=0,461) survival rates.

CONCLUSIONS. Both overall and graft survival rates after liver transplantations performed in the Department of General, Transplant and Liver Surgery in cooperation with the Department of Immunology, Internal Medicine, and Transplantology at the Transplantation Institute Medical University of Warsaw in patients with HBV and HCV infection are comparable to those reported by other European and American centers. In contrast to other studies, obtained results do not confirm the negative impact of HCV infection on long-term outcomes of patients.

Key words*: liver transplantation, hepatitis B virus, hepatitis C virus, outcomes*

INTRODUCTION

The consequences of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are one of the most common causes of end-stage liver disease in the world.However, there are major differences in the frequency, natural history, and available methods of treatment between both viruses. It is estimated that in 2005, chronic infection, defined as the presence of HBs antigen in serum, affected about 240 million people worldwide (1). Approximetely 8-20% of patients with chronic hepatitis B virus infection develop liver cirrhosis in a 5-year follow-up period. Treatment currently comprises the use of pegylated interferon alpha (2a and 2b), nucleoside analogues (lamivudine, telbivudine, emtricitabine, entecavir), and nucleotide analogues (adefovir, tenofovir) (2).

About 130-210 million people in the world are chronically infected with hepatitis C virus. Cirrhosis develops in 4-24% of patients after 20-40 years of chronic infection (3). Treatment is currently based on administration of both pegylated interferon alpha (a or b) and ribavirin. The effectiveness of such treatment is dependent upon many factors, most important of which is the genotype of HCV. In general, successful outcome is achieved in 60% of patients. More specifically, the corresponding rates are 40-50% for genotype 1 (most common in Poland) and 70% for genotype 3. Currently, registered two NS3 protease inhibitors (boceprevir and telaprevir), which significantly improve the results of treatment of chronic hepatitis C have been registered. Many other therapeutic agents are currently being investigated, ie. polymerase NS5A and NS5B inhibitors, cyclophilin inhibitors, and new types of interferon (4).

Considering similar transmission patterns of HCV and HBV, coinfection remains a major clinical issue. Although coinfection is associated with inhibitory effects regarding both HCV and HBV replication, several studies indicated more severe clinical course as compared with isolated infection (5-7). Treatment of chronic HCV infection in the case of HBV co-infection is associated with a higher risk of recurrence and lower rate of ALT normalization than in cases of isolated HCV infection (8).

Liver transplantation is the only available effective treatment in patients with end-stage liver disease. Importantly, viral cirrhosis remains the most frequent indication for transplantation both in Europe and USA (9,10). In patients with viral cirrhosis, recurrence of infection markedly influences post-transplant survival. Regarding patients with HBV infection, widespread introduction of prophylaxis based on specific immunoglobulin and nucleotide or nucleoside analogues has led to significant reduction of the risk of recurrence and improvement of long-term survival (11). On the other hand, post-transplant HCV recurrence is observed in the vast majority of patients (12). Natural history of post-transplant HCV recurrence is characterized by increased progression to fibrosis and more frequent graft failure due to the immunosuppressive therapy (13). Accordingly, long-term outcomes of patients with chronic HCV infection after liver transplantation are inferior to those with other etiologies of end-stage liver disease (14,15).

The aim of this study was to compare long-term results of liver transplantation between patients with isolated HBV infection, isolated HCV infection, and HBV/HCV coinfection basing on the material of the Department of General, Transplant and Liver Surgery at the Medical University of Warsaw.

MATERIAL AND METHODS

There were 1090 liver transplantations performed in the period between December 1994 and May 2012 in the Department of General, Transplant and Liver Surgery in cooperation with the Department of Immunology, Transplantology and Internal Diseases of the Medical University of Warsaw (fig. 1). 1030 of these were primary transplantations and 60 were retransplantations. Most frequent etiologies of the end-stage liver disease among recipients of primary transplantations were HCV and HBV infection, alcohol, and autoimmune diseases (fig. 2).

This study was performed on a historic cohort of patients after liver transplantation due to end-stage liver disease related to chronic HCV and/or HBV infection. Patients with malignant tumors (hepatocellular cancer, cholangiogarcinoma, combined hepatocellular/cholangiocellular cancer, carcinosarcoma, lymphoma)

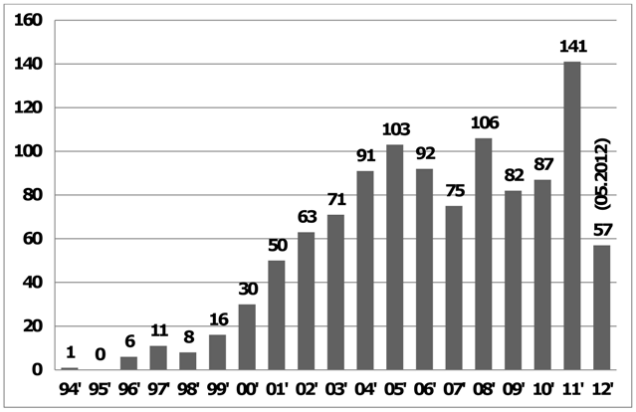

Fig. 1. Annual number of liver transplantations performed in the Departmentof General, Transplant and Liver Surgery in cooperation with the Department of Immunology, Internal Medicine, and Transplantology at the Transplantation Institute (Medical University of Warsaw) between December 1994 and May 2012

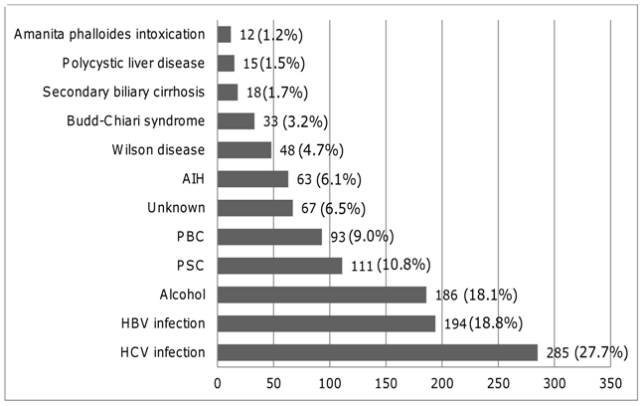

Fig. 2. Etiology of liver disease in a total of 1030 recipients of primary transplantation

fulminant hepatic failure in the course of HBV infection, and coexisting etiologies of end-stage liver disease (other than HBV/HCV) infection were excluded from the study.

Although HCV and HBV infection was present in respectively 285 and 194 out of a total of 1030 recipients of primary transplantations, 209 patients were finally included in the study using the previously defined criteria. These patients were further divided into 3 groups: group I - (n=56) – patients with isolated HBV infection, group II (n= 119) – patients with isolated HCV infection, group III (n= 34) – patients with HBV/HCV coinfection.

Groups were compared with respect to the following variables: recipient' age and gender, Model for End-Stage Liver Disease (MELD) score, donor' age, and cold ischemic time. Evaluation of long-term outcomes was based on the 5-year overall and graft survival rates. Overall survival was defined as time between transplantation and death. Graft survival was defined as time between transplantation and retransplantation or death. Both overall and graft survival rates were compared between groups.

Variables were presented as median and ranges or as numbers and percentages, wherever appropriate. Kruskal-Wallis test and Fisher's exact test were used to compare parametric and nonparametric variables, respectively. Five-year overall and graft survival rates were estimated on the basis of Kaplan-Meier method. Reverse Kaplan-Meier method was applied for calculation of median follow-up. Survival curves were compared with log-rank test. Statistical significance level was set at 0.05. All analyses were computed in Statistica v. 8.0 (StatSoft) and SAS (Sas Institute).

RESULTS

Majority of the recipients were males (n=127; 60.8%). Median age was 48 years. Baseline characteristics of the study cohort are presented in Table I. There were no statistically significant differences between

Table I. Baseline characteristics of the study cohort

Variables	Number (%) or median (range)
Recipient gender	
Male	127 (60.8%)
Female	82 (39.2%)
Recipient age	48 (17-67)
MELD score	13 (6-47)
Donor age	45 (14-67)
Cold ischemic time (h)	9.0 (3.3-14.0)

Table II. Comparison of baseline characteristics between patients within different subgroups.

Variables	Group I HBV+/HCV-	Group II HBV-/HCV+	Group III HBV+/HCV+	*P*
Recipient gender				0.423
Male	38 (67.9%)	70 (58.8%)	19 (55.9%)	
Female	18 (32.1%)	49 (41.2%)	15 (44.1%)	
Recipient age	49 (17-65)	49 (20-67)	45 (17-58)	0.011
MELD score	14 (6-45)	12 (6-42)	13.5 (8-47)	0.328
Donor age	43.5 (14-63)	43 (15-63)	48.5 (20-67)	0.114
Cold ischemic time (h)	9.0 (3.3-13.7)	9.0 (3.5-13.3)	9.3 (3.5-14.0)	0.716

Data are presented as number (%) or median (range).

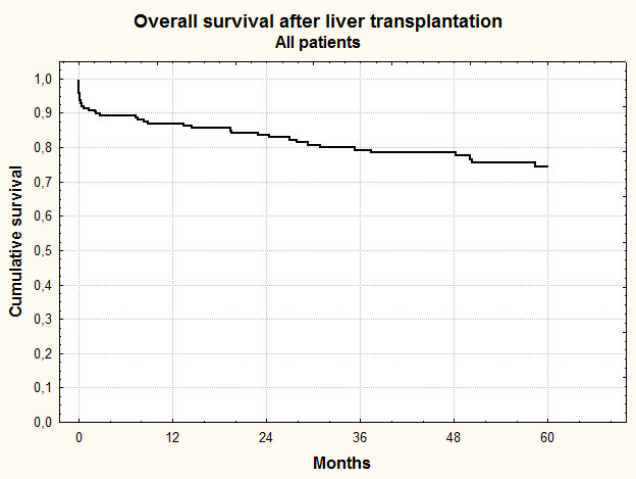

Fig. 3. Survival of all patients included in the study

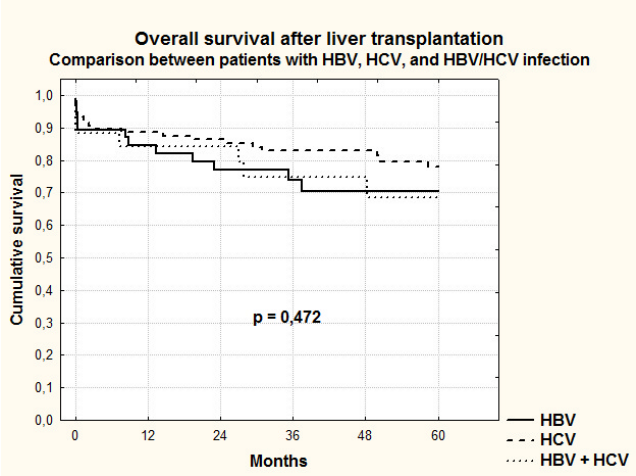

Fig. 4. Survival in 3 subgroups of patients: (i) with chronic HBV monoinfection, (ii) with chronic HCV monoinfection, and (iii) with HBV/HCV coinfection

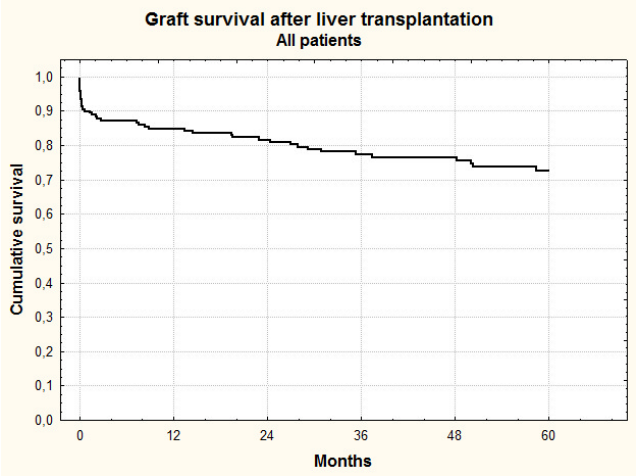

Fig. 5. Graft survival in all patients included in the study

groups with respect to recipient' gender, MELD score, donor' age, and cold ischemic time. However, recipient age was significantly different between the 3 groups, with median age being 49,49 and 45 in groups I, II, and III, respectively (Table II).

Median follow-up was 49 months. Overall survival at 1, 3, and 5 years was 86.8%, 79.2%, and 74.5%, respectively (fig. 3). In patients with isolated HBV infection (group I) 1, 3, and 5-year overall survival was 84.7%, 73.7%, and 70.4%, respectively. The corresponding rates of overall survival were 88.3%, 82.6%, and 77.8% in recipients with isolated HCV infection (group II) and 84.3%, 74.8%, and 68.5% in patients with HBV/HCV coinfection (group III, fig. 4). Observed differences in overall survival between the 3 groups did not reach the level of significance (p=0.472).

Graft survival was 84.9% after 1 year, 77.4% after 3 years, and 72.6% after 5 years in the whole study cohort (fig. 5). No significant differences regarding graft survival were observed between 3 groups of patients (p=0.461). 1, 3, and 5-year graft survival rates were: 80.7%, 70.2%, and 67.0% in group I; 86.8%, 81.3%, and 76.3% in group II; and 84.3%, 74.8%, and 68.5% in group III (fig. 6).

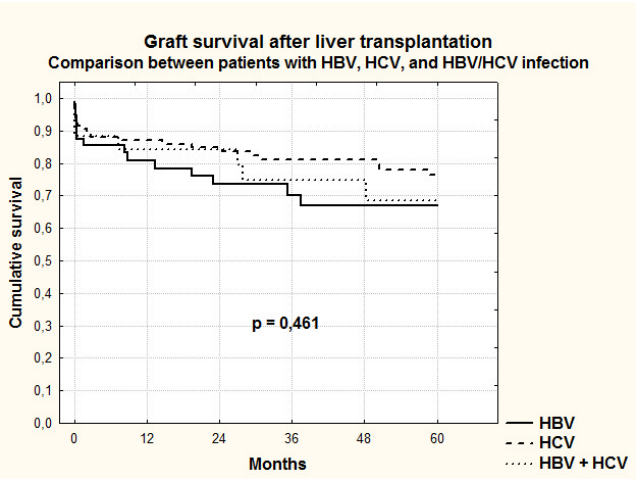

Fig. 6. Graft survival in 3 subgroups of patients: (i) with chronic HBV monoinfection, (ii) with chronic HCV monoinfection, and (iii) with HBV/HCV coinfection

DISCUSSION

Results presented in this study are based on 18-year experience of the largest liver transplant center in Poland. Development of liver transplant program in the Department of General, Transplant and Liver Surgery in cooperation with the Department of Immunology, Transplantology and Internal Diseases at the Medical University of Warsaw has led to more than 10-fold increase in the annual number of performed transplantations from the 90's to 2011 (141 in the year 2011). HCV infection predominated among all causes of end-stage liver disease among all patients treated with liver transplantation in our center, similarly to other European countries and United States of America

(9,10). However, HBV infection is markedly more frequent indication for liver transplantation in Poland than in USA, which relates to differences in the prevalence of infection with this virus . Introduction of obligatory HBV vaccination reduced markedly the number of new cases with HBV infection and will limit the number of patients requiring liver transplantation.

Exclusion of patients with end-stage liver disease of mixed etiology and patients with malignant tumors was done in order to obtain more homogeneous study population, more appropriate for analyses addressing the study's aims. Notably, development of hepatocellular cancer (HCC) is one of the most important factors influencing the prognosis of patients with cirrhosis related to HBV and/or HCV infection. However, liver transplantation for HCC is a separate issue in transplantology exceeding the scope of the presented paper (16).

Overall survival rate of 74.5% together with graft survival rate of 72.6% correspond to the data from the largest liver transplant registries. Five-year overall survival in a cohort of over 19.5 thousand patients from the European Liver Transplant Registry (ELTR) after liver transplantation for viral cirrhosis is currently 69% (9). According to recent UNOS annual report 5-year graft survival in patients after liver transplantation for end-stage liver disease related to HCV infection does not exceed 65% (data on outcomes of patients with HBV infection after liver transplantation were not included in this report) (10). Achievement of long-term results of liver transplantation comparable or even slightly higher than those reported by the largest transplant centers worldwide mirrors the increasing experience of the transplant team of the Department of General, Transplant and Liver Surgery and the Department of Immunology, Transplantology and Internal Diseases at the Medical University of Warsaw. Both departments listed above were involved in the performance of approximately 1100 liver transplant procedures over an 18-year period. Of note, increasing experience of the transplant team has been reported previously (17).

In contrast to the results of other studies available in the transplant literature indicating inferior outcomes of liver transplant recipients with HCV infection, no significant differences were found with respect to overall and graft survival rates between patients with isolated HBV infection, isolated HCV infection, and HBV/HCV coinfection (14,15). Moreover, results of liver transplantations in patients with isolated HCV infection were non-significantly better than in the remaining recipients. Therefore, these observations confirm the results of our recently published study based on the first 1000 liver transplantations performed in the Department of General, Transplant and Liver Surgery showing no significant differences in outcomes of recipients with and without HCV infection (18).

Donor age has a major impact on the risk of post-transplant HCV recurrence (19). According to Mutimer et al., the negative impact of recipient' HCV infection on survival after liver transplantation is observed only for donor age exceeding 50 years (20). Thus, superior outcomes of recipients with HCV infection reported in the present study might relate to the lower median age of donors (43 years) as compared to other available studies (14,15).

There are two aspects of the association between HBV/HCV coinfection and long-term outcomes of patients after liver transplantation. First, coinfection with both viruses might lead to earlier development of graft failure (21,22). On the contrary, inhibitory effects of HBV on HCV replication might decrease the risk of post-transplant HCV recurrence (7,23). In a retrospective study by Waki et al. based on more than 48 thousand liver transplantations from the UNOS registry, graft survival rate at 10-years was lowest for the recipients with isolated HCV infection, intermediate for the recipients with HBV/HCV coinfection, and highest for the recipients with isolated HBV infection (24). Conversely, survival outcomes reported in the present study were similar between recipients with isolated HBV infection and recipients with HBV/HCV coinfection.

Notably, there are many significant prognostic factors for long-term results of liver transplantation other than etiology of the liver disease, including MELD score, donor age, and cold ischemic time (25). Comparisons between the 3 groups revealed no statistically significant differences between these variables.

CONCLUSIONS

Long-term results of liver transplantations performed in the Department of General, Transplant and Liver Surgery in cooperation with the Department of Immunology, Transplantology and Internal Diseases at the Medical University of Warsaw in patients with chronic HBV and/or HCV infection are comparable to European and US data. Overall and graft survival rates are similar in recipients with isolated HCV infection, isolated HBV infection, and HBV/HCV coinfection in a 5-year follow-up period.

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