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Malignancy in the HIV-Infected Patient Undergoing Liver and Kidney Transplantation

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Abstract

Purpose of review—The transplant community has seen gradual acceptance of liver and kidney transplantation (LT, KT) in carefully selected HIV positive patients. The addition of transplant immunosuppressants to an already immunocompromised state, however, may increase the risk of malignancy.

Recent findings—KT and LT have been successful in large series of carefully selected HIV infected patients, with graft and patient survival approaching those of non-HIV infected patients. The incidence of acute cellular rejection (KT) and of recurrent hepatitis C (LT) remains challenging. Hepatocellular carcinoma, which is a common indication for LT, seems to occur at a younger age and to have a generally worse outcome in the HIV+ patient. LT outcomes for HCC in these patients, however, do not seem to be compromised. Rates of Kaposi's sarcoma (KS) and other de novo malignancies such as skin cancer are relatively low after transplant. KS may regress with use of the mTOR inhibitor sirolimus. In HIV+ patients followed closely for HPV-related anal neoplasia after transplantation there may be an increased risk of progression to high grade squamous intraepithelial lesions.

Summary—The risk of recurrent or de novo malignancy after solid organ transplantation in HIV patients is low. HPV-related neoplasia, however, requires further study.

Keywords

Human Immunodeficiency Virus; Transplantation; Malignancy; Hepatocellular carcinoma

Until recently, the benefits of solid organ transplantation for the treatment of end stage liver and kidney disease were denied the HIV infected patient because of fears that the surgery itself or the subsequent immunosuppressive requirements would exacerbate progression of HIV and associated sequelae. The development of combination anti-retroviral therapy

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(cART) has dramatically improved long term control of HIV, which has been accompanied by greater numbers of patients with long term exposure to hepatitis B and C, and in turn greater numbers of patients with cirrhosis, end stage liver disease and hepatocellular cancer. Several factors have led to increased numbers of HIV infected patients with end stage kidney disease, including long term exposure to HIV medications, co-infection with HCV and an overall aging population. The disease burden of end stage organ failure combined with growing confidence in the efficacy of HAART has led many centers to begin offering solid organ transplantation to HIV infected patients under strict selection criteria with the expectation of sustained post-transplant control of HIV, and the number of published reports of transplantation in this patient group continues to steadily increase.

The selection criteria for solid organ transplantation in HIV infected patients include at a minimum evidence of sustained control of HIV, a reasonably well-preserved CD4 count and the absence of significant active opportunistic infection or neoplasia (Table 1). Most of the remaining selection criteria for liver or kidney transplantation (LT, KT) in HIV infected patients are similar to those in non-HIV infected patients, although debate over the value of LT in the setting of hepatitis C virus (HCV) co-infection continues and is covered below. Most importantly, because of the complex interactions between anti-retroviral therapy and immunosuppressive medications and because of the potential confounding factors that HIV infection introduces, solid organ transplantation should only be undertaken at centers with extensive HIV experience and with well-functioning multidisciplinary care teams.

The largest series to date of solid organ transplantation in HIV infected patients is an ongoing NIH-funded US multicenter prospective trial (HIV-TR) in which 150 HIV + patients underwent KT and 125 patients underwent LT between 2003 and 2010 [1]. In this study, patients undergoing kidney transplantation had a 1 and 3-year patient survival of 94% and 88%, and 1 and 3-year graft survival of 90% and 74% respectively [2]. These graft survival rates were felt to be acceptable but slightly below that seen in historical non-HIV infected patients, likely due to higher rates of acute rejection. Sustained control of HIV viral load after transplant was excellent, with only 5 cases of HIV-related neoplasia or HIV progression noted.

In patients undergoing liver transplantation in the HIV-TR study, the outcomes of LT for hepatitis B were excellent, with 3 years patient survival of 85% [3]. However, In patients with HCV/HIV coinfection, the patient and graft survival rates were lower, with 3-year patient and graft survival of 60% and 53% respectively. This survival rate was significantly lower than that seen in a matched control group of non-HIV HCV patients [4]. Several factors were identified which increased the risk of graft loss in HIV/HCV infected patients, including older donor age, combined liver/kidney transplant, use of an HCV positive donor and a body mass index of under 21 in the recipient. In HIV/HCV patients without these risk factors, the 3-year patient survival was similar to that of non-HIV infected patients undergoing LT for HCV, leading to the conclusion that LT in the HIV/HCV patient can be safely undertaken with careful donor and recipient selection. In this more recent report from the HIV-TR study, there were again no deaths attributable to HIV progression or opportunistic infection.

In a recent review and meta-analysis of liver transplant outcomes in HIV-infected patients, Cooper et al. analyzed individual data from 15 cohort studies and 49 case series [5]. This study identified 686 patients undergoing liver transplantation and found overall survival at 1, 3 and 5 years of 85%, 66% and 64% respectively. Further analysis of a subset of these patients found markedly better survival in patient with hepatitis B/HIV coinfection (compared to those without hepatitis B) and worse survival in those with detectable HIV viral load at the time of transplant. The presence of hepatitis C predicted worse overall survival in unadjusted analysis, but was not associated with worse survival when adjusted for other confounding variables.

Specific analysis of the immune system after LT in the HIV patient has been undertaken by several investigators. Samri et al as part of the THEVIC trial in France reported on the immune responsiveness in HIV/HCV patients after LT and found that anti-HCV responsiveness as well as immune competence against HIV and opportunistic pathogens such as candida was preserved in patients who were receiving a tacrolimus and steroid based immunosuppressive regimen. Patients with aggressive HCV recurrence after LT lacked the immune responsiveness to HCV, suggesting a dire need for better HCV treatments after LT in the subset with deficient HCV immunocompetence [6].

Hepatocellular Cancer and HIV

Hepatocellular carcinoma is the fourth leading cause of cancer death worldwide, with over 1 million new cases diagnosed worldwide yearly. The primary risk factor for HCC is the presence of cirrhosis, although HCC commonly develops in the patient with hepatitis B even without underlying cirrhosis. The same factors that have led to increasing numbers of HIV+ patients presenting with end stage liver disease are leading to increased occurrence of HCC, as co-infection with HCV and HBV puts these patients at risk for cirrhosis and in turn HCC.

There is a growing body of evidence that the pattern of occurrence of HCC is different in the HIV-infected patient than in the non-HIV patient. A recent French observational study by Bourcier et al analyzed two cohorts of liver cancer, those with HIV-HCV co-infection and those with HCV alone [7]. In this study, HCC occurred at a younger age in those with HIV-HCV co-infection (48 years old vs. 60 years old) and presented at a more advanced stage and was associated with worse outcome in the HIV-HCV group. An Italian observational study which compared HIV infected to non-infected patients also reported mean age at time of occurrence is younger in the HIV patient. This study did not find tumors to be more advanced in HIV patients at presentation, but found significantly shorter survival times and fewer attempts at cancer retreatment in HIV patients [8].

These reports and several similar reports have led to assertions that HIV is itself a risk factor for HCC in patients with underlying liver disease, and that it may be more aggressive and more lethal in the HIV infected patient. In a review of a large cohort of HIV patients followed prospectively in France, Bruyand et al reported that CD4 counts < 500 were associated with higher incidence of HCC, but that the overall duration of immunodeficiency was not associated with increased risk [9].

Liver Transplantation for HCC

Liver transplantation as a treatment for HCC is an attractive option because it simultaneously addresses the hepatic tumor burden as well the underlying liver disease and liver dysfunction. Risk of recurrent HCC after LT is largely related to the stage and morphology of the tumor at the time of transplant, as *de novo* HCC should no longer form in the absence of the “fertile soil” of the pre-transplant cirrhotic liver. LT has been widely accepted as a valuable treatment for HCC in patient with cirrhosis since the landmark paper by Mazzaferro, et al [10] which reported survival rates of 75% at 4 years in patients undergoing LT for HCC that was within Milan criteria (consisting of single hepatic lesion ≤ 5 cm, or 2 or 3 lesions ≤ 3 cm).

Despite the worldwide acceptance of LT for HCC that is within Milan criteria, few reports have been published on LT in HIV positive patients with HCC. In a recent study from France, Vibert et al reported on 16 HIV + patients undergoing liver transplantation for HCC and found no significant difference in overall survival or recurrence-free survival compared to 58 non-HIV patients with HCC from the same time period [11]. Most patients were within Milan criteria. Three year overall and recurrence-free survival in the HIV-HCC patients in this report were 85% and 74% compared to 93% and 81% respectively in a non-HIV patient group. Similar to other studies, the HIV-HCC patients in this transplant population were younger than their non-HIV counterparts (48 years vs. 57 years) and had higher alpha-fetoprotein levels. The drop-out rate, or the number of patients who were listed for LT but ultimately were not able to undergo LT, was suggested to be higher in the HIV positive group, with 5 of 21 listed patients dropping out due to tumor progression (n=4) or HIV progression (n=1). Five of 16 patients (31%) experienced HCC recurrence at a median 11 months post-LT which was not significantly greater than in the non-HIV/HCC group (p=. 15). The authors in this report favored cyclosporine immunosuppression and did not routinely alter their immunosuppressive regimen in the HIV/HCC patients.

In a report from the University of Modena, investigators describe performing liver transplantation in 23 patients with HIV coinfection, including 14 patients with HCC. Ten of these 14 patients were within Milan criteria and 4 were outside of Milan criteria. No cases of recurrence are reported, but 10 patients died overall. Cause of death was primarily due to recurrent hepatitis C or infectious complications for an overall patient and graft survival at 80 months of 50% and 45% respectively. The authors report favoring an immunosuppressive regimen of the mTOR inhibitor rapamycin over calcineurin inhibitors in the HIV/HCC LT patients, presumably due to possible antitumor effects of rapamycin. One patient with post-LT Kaposi’s sarcoma had resolution of lesions after conversion to rapamycin [12].

In the HIV-TR study, HCC (majority within Milan criteria) was present in 45 (36%) of the 125 liver patients undergoing LT. HCC recurrence has been seen in 2 patients at a median follow-up of 34 months. The majority of patients in this report were maintained on calcineurin-inhibitor-based immunosuppressive regimens.

These reports demonstrate the utility of LT as a treatment for HCC in the HIV infected patient. Careful patient selection is critical, primarily related to the risk factors for recurrent

HCV infection noted above. The majority of evidence, however, suggests that in appropriately selected patients the risk of recurrent HCC after LT in the HIV+ patient is low. The use of mTOR-based immunosuppressive strategies in the HIV-HCC patient after LT is compelling but not universally practiced, and at present there is little data to support routine use of rapamune or similar agents over the more commonly utilized calcineurin inhibitor-based regimens. In addition, there is no data on the use of the multi-kinase inhibitor sorafenib in the treatment of HCC in the HIV+ patient.

Neoplasia after Transplantation in the HIV patient

Solid organ transplantation brings with it the need for lifelong immunosuppressive therapy. One of the concerns over transplantation in the HIV+ patients is that the addition of immunotherapy to the already immunosuppressed patient would lead to increased neoplasia, either in the form of recurrent malignancies (such as in the patient transplanted for HCC) or new malignancies. In the ongoing HIV-TR trial of 275 total transplant patients, 25 patients (9%) developed post-transplant malignancy and 7 patients (3%) died from a cancer-related cause. In the group undergoing KT, 13 out of 150 patients (8.7%) had developed 14 malignancies at a median follow-up of 3.5 years post-transplant. This included skin cancer (n=5), cutaneous Kaposi's sarcoma (n=3), penile squamous cell cancer (n=1), head and neck cancer (n=3) and renal cell cancer (n=2). There were 3 CA related deaths in KT. In 125 patients undergoing LT in this study, 12 patients developed 14 malignancies at a median follow-up of 2.8 years post-transplant. De novo malignancies in this group included skin cancer (n=9), Kaposi's sarcoma (n=1) and lymphoma (n=1). Three patients had recurrence of pre-LT malignancy, including 2 HCC and 1 cholangiocarcinoma.

At present, the incidence of malignancy after solid organ transplantation in the HIV infected population does not appear to be significantly different than that seen in non-HIV-infected patients. Kaposi's sarcoma, thought to be driven at least in part by HHV8 proliferation related to the immunosuppression that accompanies transplantation, was recently reported to occur at a rate of approximately 2% after LT [13], similar to that in the HIV-TR report. All de novo KS lesions in the HIV-TR study were cutaneous, and all were treated successfully with the addition of rapamycin to the immunosuppressive regimen. Rapamycin, a TOR-inhibitor used as an alternative immunosuppressive agent, also has well documented therapeutic effects on KS [14] Similarly, the rates of de novo head and neck cancers and of recurrent HCC after LT are relatively low in the HIV-TR study and other similar reports, and are in line with those rates reported in non-HIV transplant populations [15].

Another goal of the HIV-TR multicenter study was to prospectively monitor the progression of human papilloma virus (HPV)-associated neoplasia in HIV infected patients undergoing solid organ transplantation. In 89 patients followed prospectively for anal cytology, there was increased risk of developing high-grade squamous intraepithelial lesions (HSIL) after transplantation. The development of HSIL in these patients was not influenced by the type of organ transplant (kidney versus liver) or by the use of T-cell depleting agents. Clearly this group requires further study to determine the longitudinal impact of transplant-related immunosuppression on HPV-related neoplasia.

Summary

HIV infection is no longer a contraindication to solid organ transplantation. Control of HIV infection has been excellent in most studies, but the recurrence rate of HCV after LT continues to be a difficult problem. Most aspects of the management of malignancy in the HIV infected transplant patient parallel that of the non-HIV infected patient. Further investigation into the effects of transplant on risk of neoplasia, particularly HPV-related neoplasia, is needed. The benefits of alternate or investigational immunosuppressive regimens on HIV or HCV progression post-transplant are intriguing but at present unproven.

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References

1. Solid Organ Transplantation in HIV: Multi-Site Study. Bethesda (MD): National Library of Medicine (US); 2000. ClinicalTrials.gov [Internet]. Available from: http://clinicaltrials.gov/ct2/show/NCT00074386 NLM Identifier: NCT00074386. [cited 2012 April 01]
2. Stock PG, Barin B, Murphy B, et al. Outcomes of kidney transplantation in HIV-infected recipients. N Engl J Med. 2010 Nov 18; 363(21):2004–2014. Erratum in: N Engl J Med. 2011 Mar 17;364(11): 1082. [PubMed: 21083386] This study describes the outcomes of 150 HIV+ patients undergoing Kidney transplant in a US multicenter trial. Patient and graft survival results are reported and are excellent, and although acute cellular rejection was common, HIV progression was rare.
3. Coffin CS, Stock PG, Dove LM, et al. Virologic and clinical outcomes of hepatitis B virus infection in HIV-HBV coinfected transplant recipients. Am J Transplant. 2010 May; 10(5):1268–1275. Epub 2010 Mar 19. [PubMed: 20346065]
4. Terrault NA, Roland ME, Schiano T, et al. Outcomes of liver transplantation in HCV-HIV coinfected recipients. Liver Transpl. 2012 Feb 12. This study describes outcomes in HIV/HCV co-infected patients, with higher rates of acute rejection seen in those with coinfection compared to HCV infection alone.
5. Cooper C, Kanters S, Klein M, et al. Liver transplant outcomes in HIV-infected patients: a systematic review and meta-analysis with synthetic cohort. AIDS. 2011 Mar 27; 25(6):777–786. [PubMed: 21412058]
6. Samri A, Roque-Afonso AM, Beran O, et al. Preservation of immune function and anti-hepatitis C virus (HCV) immune responses after liver transplantation in HIV-HCV coinfected patients (ANRS-HC08 "THEVIC" trial). J Hepatol. 2009 Dec; 51(6):1000–1009. Epub 2009 Sep 12. [PubMed: 19833404]
7. Bourcier V, Winnock M, Ait Ahmed M, et al. Primary liver cancer is more aggressive in HIV-HCV coinfection than in HCV infection. A prospective study (ANRS CO13 Hepavih and CO12 Cirvir). Clin Res Hepatol Gastroenterol. 2011 Dec 19. This report describes the profile with HCV and suggests a more aggressive behavior of tumor in those with HIV coinfection.
8. Berretta M, Garlassi E, Cacopardo B, et al. Hepatocellular carcinoma in HIV-infected patients: check early, treat hard. Oncologist. 2011; 16(9):1258–1269. Epub 2011 Aug 25. [PubMed: 21868692]
9. Bruyand M, Dabis F, Vandenhende MA, et al. HIV-induced immune deficiency is associated with a higher risk of hepatocarcinoma, ANRS CO3 Aquitaine Cohort, France, 1998–2008. J Hepatol. 2011 Nov; 55(5):1058–1062. Epub 2011 Feb 25. [PubMed: 21354449]
10. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996 Mar 14; 334(11):693–699. [PubMed: 8594428]

11. Vibert E, Duclos-Vallée JC, Ghigna MR, et al. Liver transplantation for hepatocellular carcinoma: the impact of human immunodeficiency virus infection. Hepatology. 2011 Feb; 53(2):475–482. Epub 2011 Jan 3. [PubMed: 21274869] This specific report compares HIV vs. non-HIV patients with hepatocellular carcinoma and shows similar outcomes between the groups.
12. Di Benedetto F, Tarantino G, De Ruvo N, et al. University of Modena experience in HIV-positive patients undergoing liver transplantation. Transplant Proc. 2011 May; 43(4):1114–1118. [PubMed: 21620066] This report describes an Italian cohort of HIV+ patients undergoing liver transplantation and shows overall excellent outcomes with low risk of post-transplant HIV progression
13. Di Benedetto F, Di Sandro S, De Ruvo N, et al. Kaposi's sarcoma after liver transplantation. J Cancer Res Clin Oncol. 2008 Jun; 134(6):653–658. Epub 2007 Oct 9. [PubMed: 17922290]
14. Stallone G, Schena A, Infante B, et al. Sirolimus for Kaposi's sarcoma in renal transplant recipients. N Engl J Med. 2005; 352:1317–1323. [PubMed: 15800227]
15. Engels EA, Pfeiffer RM, Fraumeni JF Jr, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011 Nov 2; 306(17):1891–1901. [PubMed: 22045767]

Outline

Update of Solid Organ Transplant in HIV+ patients

HCC in the HIV positive patient

LT for HCC in the HIV positive patient

Denovo and recurrent malignancy after solid organ transplantation in the HIV + patient

Key Points

Kidney and liver transplantation are successful in carefully selected HIV positive patients, with graft and patient survival approaching those of non-HIV infected patients.

HIV positive patients undergoing liver transplantation for hepatocellular carcinoma have low recurrence rates and generally fair as well as non-HIV infected patients.

De novo malgnancies including skin cancer and Kaposi's sarcoma can occur after solid organ transplantation in these patients, but do not appear to occur with increased incidence.

Preliminary results suggest that human papilloma virus mediated-anal lesions may have an accelerated progression after transplantation. This requires more study.

Table 1

Exclusion Criteria for Liver for Kidney Transplantation in HIV Positive Patients

Medical or psychosocial contraindication to transplantation
CD4 count < 200 (or < 100 for liver)
Detectable HIV viral load (unless HAART therapy held due to hepatotoxicity
Multidrug resistant HIV or unstable HAART regimen
Recent malignancy other than hepatocellular carcinoma
Active opportunistic infection*
Substantial wasting
History of progressive multifocal leukoencephalopathy, chronic cryptosporidosis, AIDS

* Pulmonary coccidiomycosis patients must be disease free 5 years