Hepatitis C: Treatment Options for the Non-Responder

Sean Koppe, MD

Hepatitis C is the leading cause of cirrhosis and the major reason for liver transplantation in the United States. At least 3 million individuals are infected with the hepatitis C virus (HCV). Approximately 80 percent of patients who are initially exposed to the virus will develop chronic infection and 20 percent of these cases will evolve into cirrhosis. The current standard treatment of HCV consists of pegylated interferon (PEG) and ribavirin (Figure 1).

Aims of Therapy
The goal of treatment is to achieve a sustained viral response (SVR), defined as a persistently undetectable level of HCV RNA six months after the end of a treatment course. Individuals achieving this goal experience fewer symptoms, have decreased hepatic inflammation and may be cured of the infection. Factors besides genotype that affect outcome are considered here. These include patient compliance, appropriate dosing of medications and the type of regimen initially used to treat the virus.

Non-Responders and Relapers
A frequent challenge is management of non-responders and relapers. A non-responder is a patient who fails to achieve an undetectable level of HCV RNA by the end of a treatment course, and a relaper is a patient who has undetectable HCV RNA at the end of a treatment course but ultimately experiences a return of detectable HCV RNA. When re-treatment is attempted, the relaper and the non-responder who had a significant reduction of HCV RNA during treatment fare better than the patient who had no change in viral load during initial treatment.

Managing Treatment Failures
The first question when approaching these patients is whether the currently recommended regimen of PEG plus ribavirin was used. Regimens that use non-PEG interferon with or without ribavirin are clearly less effective than currently available therapy. Re-treatment with PEG plus ribavirin of a non-responder who previously received standard interferon with or without ribavirin can result in an SVR of up to 30 percent. Relapers fare better when re-treated with PEG plus ribavirin, with an SVR of up to 50 percent.

Patient motivation, extent of fibrosis and tolerance of previous therapy are important factors in the decision to attempt re-treatment with PEG plus ribavirin.

If patients are non-responders or relapers despite the currently recommended regimen of PEG plus ribavirin, then physicians must consider whether the appropriate dose of medication was utilized, if the duration of treatment was adequate and if the patient was fully compliant. Patients have a lower chance of achieving an SVR if they receive less than 80 percent of the recommended dose of either PEG or ribavirin or less than 80 percent of the total treatment duration. Dose reductions during the initial weeks of therapy can have a particularly adverse effect. Side effects that limit optimal treatment include depressed mood, irritability, muscle aches, fatigue and cytopenias. These side effects are most pronounced in the initial weeks and typically improve with time, but in some patients they result in early discontinuation of treatment or reduction of PEG to a less effective dose. Cytopenias can be managed with aggressive use of growth factors such as erythropoietin or granulocyte colony stimulating factor.

An additional consideration is the patient’s weight, since therapy is less effective in obese patients. One strategy may be re-treatment with doses of PEG and ribavirin adjusted to the patient’s weight. Whatever the reason for treatment failure, an additional approach is re-treatment with consensus interferon (CIFN). CIFN is a more potent formulation of interferon-alpha that is given daily. The downside of this therapy appears to be increased side

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Minimally Invasive Liver Resection (MILR) at Northwestern Memorial Hospital: Evolution, Experience and Outcomes

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The growing experience with laparoscopic procedures, the ongoing technological advances in laparoscopic devices and an increased patient awareness of the availability of these techniques have created an evolving interest in the application of these techniques to liver surgery and liver resection. The surgical skills required for MILR have evolved in parallel with the adaptation of laparoscopic techniques to these procedures and now include laparoscopic approaches to liver cysts, wedge resection of peripheral solid tumors and, more recently, major resections.

Methods

We made the decision to initiate an MILR program as part of our busy hepatobiliary practice, beginning with benign cystic lesions of the liver¹. We subsequently included patients with peripheral solid benign lesions, progressing to patients with malignant lesions, patients with fibrosis/cirrhosis and patients with larger magnitudes of resection. This early phase included only pure laparoscopic resections. Finally, as a means to perform formal lobectomies, hand-assisted techniques were employed until these could be performed with certain patient safety, at which time we implemented the use of pure laparoscopic techniques for lobectomies needed in resection of deeper lesions.

Because of the nature of this evolution, we have continued to perform the majority of resections using pure laparoscopic techniques, unless safety or oncologic principles are in jeopardy. In addition, we have used a laparoscopy-assisted open technique (hybrid method) in order to offer a minimally invasive approach to patients when patient safety does not allow for pure laparoscopic techniques, such as in the case of living-donor right hepatic lobectomy.

In a recent report², we noted that the evolution of MILR at our institution has shifted our approach to the management of liver tumors, especially benign tumors. In that report, we utilized specific case studies and combined our experience with that of the group at the University of Pittsburgh in order to demonstrate that the growing availability of these techniques can affect clinical decision making in the management of these tumors.

We recently published our experience with 300 consecutive patients who underwent MILR at Northwestern Memorial Hospital³. This experience constitutes the largest and most comprehensive series to date on the use of MILR for both benign and malignant liver lesions.

In order to compare MILR to traditional open liver resections, we compared these 300 cases to contemporaneous open resections also accessed from the database, attempting to match for age, type of resection, etiology and the presence or absence of cirrhosis. MILR compared favorably with standard open techniques in terms of operative times, blood loss, transfusion requirement, length of stay, overall operative complications and local malignancy recurrence. In our series, 80 percent (241 of 300) of resections were performed using pure laparoscopic techniques, with a large portion comprising benign lesions, as testament to our conservative approach to malignancy.

Conclusions

We have clearly shifted toward a more liberal use of MILR for liver tumors at our center. We currently consider MILR first as the preferred approach for all patients who require liver resection, as long as patient safety and the effectiveness of resection are not compromised.

We believe that this field will continue to advance and that eventually most liver resections will be performed utilizing a spectrum of MILR techniques. This will require that surgeons are satisfied that the risks to the patient associated with MILR are at most equivalent to those of open resection. In addition, a more generalized shift toward MILR also will require an increased recognition by surgeons that MILR is associated with less morbidity and better cosmetic effect than open procedures. We hope our published reports will contribute to this development. In the meantime, groups such as ours will continue to apply these techniques with the conviction that patients derive significant benefits, including smaller incisions, shorter hospital stays and less morbidity, from minimally invasive procedures when compared to their open counterparts.

REFERENCES:

Liver Transplantation for HIV-Infected Patients

Valentina Stosor, MD

The availability of highly active antiretroviral therapies (HAART) has had a tremendous impact on the natural history of human immunodeficiency virus (HIV) infections, with dramatic reductions in opportunistic infections and mortality in patients with this infection. However, end-stage liver disease has emerged as a significant complication and a leading cause of death among long-term survivors of HIV infection.¹

In the pre-HAART era, HIV infection was an absolute contraindication to organ transplantation due to rapid progression of HIV with the additive immunosuppressive effects of anti-rejection therapies. Now, with the reality of long-term HIV suppression, liver transplantation is emerging as a treatment option for patients with advanced liver disease. Published preliminary studies of liver transplantation in the setting of HIV infection have demonstrated short-term patient outcomes and graft survival that compare favorably with that of the general transplant population. The National Institutes of Health is sponsoring a prospective clinical trial to critically evaluate the safety and efficacy of liver transplantation in HIV-infected patients. The Northwestern Memorial Hospital Liver Transplant Program is one of 20 sites participating in this study.

Causes of Liver Disease in Patients with HIV Infection

Hepatitis C (HCV) and B (HBV) viral coinfection are leading causes of liver-related morbidity and mortality in HIV-infected persons. The incidences of hepatitis co-infections with HIV are up to 24 to 35 percent for HCV and 9 percent for HBV. HIV infection, especially the associated CD4 lymphopenia, promotes progression of chronic viral hepatitis to end-stage liver disease, and antiretroviral drug hepatotoxicity can complicate the course of liver disease. Non-viral causes of progressive liver disease, such as the long-term consequences of drug hepatotoxicity, also are described in these patients.²

Indications for Referral for Liver Transplantation

Patients with HIV and advanced liver disease are at higher risk for death compared with uninfected patients after a first episode of decompensation. In this patient population, mortality is not predicted by the severity of liver disease as measured by the Model for End-Stage Liver Disease (MELD) or Child-Pugh scores. Because of this, early referral is imperative, particularly when patients develop ascites, hepatic encephalopathy or bleeding from varices.

This disparity between mortality and MELD scores also results in excessive deaths among HIV-infected patients who are waiting for a transplant, underscoring the need for ongoing highly specialized care. Living-donor transplantation may be an important option for patients with low MELD scores, but the benefit must be weighed against the risk of right hepatic lobe donation. Northwestern Memorial has assembled a multidisciplinary surgical and medical team to handle the complex issues that HIV-infected patients encounter before, during and after transplantation.

HIV-Specific Criteria for Transplantation

In addition to the pre-transplant evaluations required of all potential candidates, patients with HIV undergo rigorous assessments to determine the status of HIV infection and to exclude active opportunistic infections. *If history of opportunistic infection such as Pneumocystis jiroveci pneumonia, then CD4 count ≥ 200 cells/mm³.

• Meet all other criteria for transplantation

Criteria for Liver Transplant Candidacy in Patients with HIV Infection

- CD4 T cell lymphocyte count > 100 cells/mm³
- On stable antiretroviral therapy with HIV viral load ≤ 50 copies/mL
- No wasting syndrome
- No active or recent opportunistic infection (OI)
- No history of OI for which there is no therapy or limited therapy
- Meet all other criteria for transplantation

Post-Transplant Care Requires a Multidisciplinary Team Approach

As a rule, post-transplant care is complicated by significant drug interactions between the immunosuppressive medications and several antiretroviral drug classes. Intensive therapeutic drug monitoring is required in the weeks and months following transplantation and after any changes in antiretroviral or anti-rejection therapy. For example, the HIV protease inhibitors, especially ritonavir, and an important anti-rejection drug, tacrolimus, compete for metabolism through the cytochrome P450 pathway. This interaction results in dramatic reductions in tacrolimus elimination. Frequent drug level monitoring and dosage adjustments are required to avoid tacrolimus toxicity. Antiretroviral therapy is further complicated by fluctuating hepatic and renal function in the peri-transplant period. With the heightened immunosuppression that follows transplantation, HIV and transplant medicine specialists intensively monitor patients for HIV breakthrough and opportunistic infections and employ infection prophylaxis strategies that target both transplant and AIDS-related opportunistic pathogens.

Monitoring of liver allograft function similarly warrants special considerations. Patients are closely followed for rejection and early recurrence of hepatitis C. Hepatitis B breakthrough may occur as a result of lamivudine and other antiviral resistance. Finally, antiretroviral agents can play a role in post-transplant hepatic dysfunction.

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effects, so patient motivation must be high to consider this option. Limited data suggest that CIFN can achieve an SVR of up to 40 percent in prior non-responders to PEG plus ribavirin.

Novel Therapy for Treatment Failures

When re-treatment of a non-responder or relaper with PEG plus ribavirin is not considered to be beneficial, the two remaining options are enrollment in a clinical trial and observation. Observation may be reasonable when the degree of fibrosis is not advanced. Newer agents include protease inhibitors and polymerase inhibitors, which interfere with viral replication and assembly. While early data are promising, it now seems that initial regimens involving protease inhibitors or polymerase inhibitors will include PEG with or without ribavirin. Additional antiviral approaches being investigated include antibodies, immunomodulators, anti-sense compounds (sequences of nucleotides that interfere with the production of proteins critical to the life cycle of the virus), modified forms of interferon, ribavirin alternatives, anti-fibrotics and vaccines. We anxiously await the availability of these new drugs, which will undoubtedly improve outcomes with fewer side effects for all patients with hepatitis C. Northwestern Memorial frequently is involved in trials for non-responders, relapers and treatment-naive patients. For more information regarding available clinical trials, please contact Kim Sipich, project coordinator, at 312-503-0121, or visit our Web site at transplant.nmh.org.


Liver Transplantation for HIV-Infected Patients (Continued from Page 3)

Summary

Liver transplantation is an emerging therapy for patients with HIV infection and advanced liver disease. The preliminary results of reported studies are promising, but a large multi-center prospective study still is ongoing. Northwestern Memorial physicians and surgeons now are evaluating HIV-infected patients for this investigation.

REFERENCES:

Please visit www.HIVTransplant.com for further details regarding this study.

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For more information about Northwestern Memorial Hospital, please visit www.nmh.org.

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