Updates on Hepatitis B, C, and End Stage Liver Disease

Alexander Monto M.D.
Assistant Clinical Professor, Division of Gastroenterology, U.C.S.F.
Director, Liver Clinic, San Francisco VA
June 24, 2009

Overview
- Hepatitis B, importance of therapy, current treatment guidelines
- Hepatitis C, STAT-C agents
- Current management of complications of cirrhosis
- Hepatocellular carcinoma: importance of screening, efficacy of therapies

Chronic Hepatitis B Infection Worldwide
- Prevalence
  - 50 million new cases per year
  - 350-400 million chronic carriers; >75% in Asia
- 15-40% progress to cirrhosis, end-stage liver disease, or hepatocellular carcinoma
- 520,000 deaths/year related to HBV complications

Chronic Hepatitis B, U.S.
- ~2 million chronic carriers
  - 0.3% of adult population
  - 4-5,000 deaths/year related to HBV complications
- Immigration from endemic areas, including Asia, impacts the U.S. pattern of disease

MMWR 2004; 51: 1252
**Natural History of Chronic Hepatitis B**

- **Acute HBV infection**
  - <2% of cases
- **Chronic infection**
  - 15-40% of cases
  - 20-30% of children <10% of adults
- **Fulminant hepatic failure**
- **Progressive chronic hepatitis**
- **Inactive carrier state**
- **Cirrhosis**
  - 15-40% of cases
- **Death**
- **HCC**

Lok and McMahon. Hepatology 2007;45:507-539

**Hepatitis B Disease States**

- **Past Hepatitis B**
  - HBSAg- HBCAb+ HBsAb+/-
- **Chronic HBV Infection**
  - Inactive HBSAg Carrier
  - Active Chronic Hepatitis
  - HBsAg + HBeAg + Anti-HBe +/- Normal ALT 
  - Elevated ALT HBV DNA + (>20,000 IU/mL, ≥10^5 c/mL)
- **Antiviral Therapy**

**Lamivudine for Patients with Chronic Hepatitis B and Advanced Liver Disease**

- 651 patients (98% Asian, 85% male), Ishak fibrosis 4 or greater (Stage 3-4, U.C.S.F.)
- HBeAg +/-, HBV DNA+, 80% ALT >nl
- Randomized: 436 lamivudine 100mg, 215 placebo (2:1)
- Primary endpoint: liver disease progression [decompensation (incr. CPT score), variceal bleed, HCC, SBP, or death related to liver disease]
- Study stopped early (median 32 months) due to significant benefit of lamivudine

Liau Y-F et al, NEJM 2004;351:1521

**With therapy: Less Cirrhosis, Less Decompensation, Less Cancer**

End Pts HR p<0.001
Incr CPT HR p=0.02
HCC HR p=0.05

Liau Y-F et al, NEJM 2004;351:1521
**AASLD Guidelines on Chronic HBV:**
*Whom to Treat with Antiviral Therapy*

- Elevated HBV DNA levels
  - ≥2,000 IU/mL or ≥10^5 copies/mL (HBeAg+)
  - ≥20,000 IU/mL or ≥10^6 copies/mL (HBeAg-)

- Persistently elevated ALT levels
  - >2 x ULN (normal ALT: 30 IU/mL for men, 19 IU/mL for women)
  - or

- Moderate/advanced liver disease on biopsy/cirrhosis
  - Stage 2, 3 or 4 fibrosis (METAVIR)

**Current therapeutic options for chronic hepatitis B**

- FDA-approved medications
  - Interferon – Intron-A®, PEGASYS ® 180mcg sq qwk
  - Lamivudine - Epivir® 100mg qd
  - Adefovir - Hepsera® 10mg qd
  - Entecavir – Baraclude® 0.5mg qd – FDA-approved 2005
  - Tenofovir - Viread® 300mg qd – FDA-approved 2008

- Medications approved for HIV infection, also active against HBV
  - Tenofovir - Viread®
  - Emtricitabine - Emtriva®
  - Tenofovir/emtricitabine - Truvada®

**HBeAg Seroconversion after a Year of Therapy for HBeAg+ Chronic Hepatitis B**

- PegIFN
- Lamivudine
- Entecavir
- Adefovir
- Placebo

**HCC Screening: Chronic Hepatitis B**
*(incidence > 0.2% per year)*

- Asian males > 40 years old
- Asian females > 50 years old
- Africans > 20 years old
- Family history of HCC
- Cirrhosis

- Non-cirrhosis: varies depending on activity, fibrosis, etc. Subjects with high HBV DNA, HBeAg or inflammation (ALT) may be at increased risk.
Anti-Hepatitis C Therapy

- Current therapies:
  1) Interferon Alpha-2b, 3M.U. sq tiw + Ribavirin 1000-1200mg po qd in divided doses (Rebetron)
  2) PEG-Interferon Alpha-2b 1.5 mcg/kg sq qwk + Ribavirin 1000-1200mg po qd (PEG-INTRON + Ribavirin)
  3) PEG-Interferon Alpha-2a 180 mcg sq qwk + Ribavirin 1000-1200mg qd (PEGASYS + Ribavirin)
  4) Consensus Interferon 6 mcg sq tiw (9 mcg sq qd and 15mcg sq qd, +/- Ribavirin, under study)

HCV Treatment Overview

- Treatment goal: eradication of virus = serum HCV RNA negative. 
  - RVR: RNA neg 4 wks; 
  - EVR: RNA neg 12 weeks; 
  - ETR: neg end of tx; 
  - SVR: RNA neg 6 months after stopping treatment = “cure”
- Genotypes 1a/1b: 35-50% SVR to 1 year of pegylated interferon+ 1000-1200mg ribavirin
- Genotypes 2/3: 60-80% SVR to 24 weeks of pegylated interferon+ 800mg ribavirin (1000-1200 also used)
- Genotype 3, high viral load, stage 3-4 liver disease, imperfect VL decline: possible benefits to 48 wks tx in GT 2/3

Registration Trial: SVR to PEGASYS/Ribavirin

- Patients (%)
  - Genotype 1
    - PEG (40 kDa) IFN alfa-2a + Placebo
    - IFN alfa-2b + RBV
    - PEG (40 kDa) IFN alfa-2a + RBV
  - Genotype 2, 3
    - P = .001
    - P = .016
    - P = .001
  - N = 1121

Patient Number Trends and Warehousing Effects for Hepatitis C: U.S., V.A.

- U.S.: 300 million Americans, ~ 20,000 new cases per year; 15,000 deaths per year from HCV cirrhosis, 3,000 liver transplants
- U.S.: of those diagnosed, likely <30% have ever received interferon-based therapy; over half were non-responders
- V.A.: 207,798 HCV+ in care in 2007, 29,995 (14.4%) had ever received a V.A. prescription for anti-HCV therapy
STAT-C Agents (Specifically Targeted Antiviral Therapy for HCV)

- Small molecule agents designed to directly inhibit the HCV life cycle
- Oral
- Block viral replication without the systemic side effects of interferon-based therapy

Telaprevir (VX-950)

- Oral inhibitor of HCV NS3, which has protease/helicase functions

PROVE 1: Telaprevir + PegIFN/RBV in Treatment-Naïve GT 1 Patients

- Randomized, double-blind, placebo-controlled, phase IIb

Mchutchison JG et al, NEJM 2009:360:1827
PROVE 1: Telaprevir + Pegasys + RBV in Treatment-Naïve GT 1 CHC Patients:

- Nitazoxanide

  - Thiazolide (specifically, nitrothiazolamide)
  - Inhibits folate metabolism (TS, DHFR, GARFT)
  - Antimicrobial activity against helminths, protozoa (cryptosporidia, microsporidia, trichomonas, entamoeba, giardia), H. pylori, anaerobic bacteria
  - Non-toxic, little resistance
  - Now: HCV, HBV

Nitazoxanide + PegIFN +/-RBV

- Randomized, controlled, Phase II trial conducted at two centers in Egypt
- Treatment-naïve patients infected with HCV genotype 4 (N = 96)
- PegIFN alfa-2a 180 µg/wk + RBV 1000/1200 mg QD (n = 40)
- NTZ 500 mg bid (n = 28)
- NTZ 500mg bid (n = 28)
- PegIFN alfa-2a + NTZ

End of Treatment

Rossignol JF et al. Gastroenterology 2009;136:856-862

Nitazoxanide + PegIFN +/-RBV: SVR

- SVR (%)
VA Patients with Cirrhosis

33% increase in unique patients (HCV+ or -) with a diagnosis of cirrhosis from 2000-2006.

Source: VA Liver Disease Database

What are indicators of decompensation?

- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice
- Alcohol
- Hepatitis C / B
- NASH
- Cholestatic
- Autoimmune

Non-Selective Beta Blockers Do Not Prevent Development of Varices

More severe side-effects (18% vs. 6%)

Prophylactic Antibiotics Improve Outcomes in Cirrhotic Patients with GI Hemorrhage

* Significantly lower
Management of Varices / Variceal Hemorrhage

- No varices
  - No specific therapy
  - Treat underlying illness
- Varices No hemorrhage
  - Med/large: NSBB or EVL
  - Small: NSBB optional
- Variceal hemorrhage
  - Antibiotics, octreotide + EVL
  - TIPS, if failure
- Recurrent hemorrhage
  - Non-selective BB plus EVL
  - TIPS, if failure

Hepatorenal Syndrome

- 2 types: Type I: rapid development of renal dysfunction (Cr rising to >2.5mg/dl in 2 weeks): median survival 2 weeks
- Type II: slower rise, Cr >1.5mg/dl
  - Management: 1) Ensure Diagnosis
  - 2) Consider Midodrine 2.5mg po qd, Octreotide 25mcg/hr, albumin 50g/d IV
  - 3) Liver Transplantation

Vasoconstrictors can be used as a bridge to transplantation in hepatorenal syndrome

Norfloxacin in the primary prophylaxis of SBP in patients with ascites protein <1.5 g/dL plus circulatory* or liver** dysfunction

- Sanyal A et al. Gastroenterology 2008; 134:1360-8
- Fernández et al., Gastroenterology 2007; 133:818-824

* Creatinine >1.2, BUN >25 or serum Na < 130
** Child score >9 and bilirubin >3
Treatment of Ascites and Complications

- **No ascites**: No specific therapy
- **Uncomplicated ascites**: Diuretics (spironolactone-based)
- **Refractory ascites**: LVP+albumin → TIPS, Prevention of SBP
- **Hepatorenal syndrome**: Vasoconstrictors (bridge), Transplant

Hepatocellular Carcinoma (HCC)

- 5th most common cancer in the world, 626,000 new cases per year worldwide
- Risk in most cirrhotics 2-5% per year (particularly in HBV, HCV)
- Recommended screening with ultrasound>CT scan every 6 months, +/- serum AFP
- Without therapy: 81% 1-yr survival, 56% 2-yr, 21% 3-yr

VA National HCV Case Registry: Current State of HCC Screening

- 15,392 patients with ICD-9 diagnosis of cirrhosis in CCR in FY 2007 (207,000 HCV+)
- 39.8% had undergone abdominal imaging (U/S, CT, or MRI, not always for screening) and had an AFP within calendar year
- 12.0% imaging alone
- 10.3% AFP alone
- 2,031 in HCV CCR have a diagnosis of HCC (1.0%)

Liver Transplant for HCC

- Approximately half of the 6,500 liver transplants performed in the U.S. annually are in pts with HCC
- Guidelines for whom to transplant: Solitary tumor <5cm or <=3 tumors, none >3cm: 85% survival at 4 years
- The role for pre-transplant ablative techniques continues to be defined
UNOS Staging for Hepatocellular Carcinoma

T0: Tumor not found
T1: 1 nodule < 1.9 cm
T2: 1 nodule 2.0-5.0 cm; 2 or 3 nodules, all <3.0 cm
T3: 1 nodule > 5.0 cm; 2 or 3 nodules, at least one > 3.0 cm
T4a: 4 or more nodules, any size
T4b: T2, T3, or T4a plus gross intrahepatic portal or hepatic vein involvement as indicated by CT, MRI, or ultrasound
N1: Regional nodes involved
M1: Metastatic disease, extrahepatic portal or hepatic vein involvement

Modified Barcelona Clinic Liver Cancer (BCLC) Staging/Therapy

Very Early Stage
- Single <2cm

Early Stage
- Single <3cm
- 3 nodules ≤3cm

Intermediate Stage
- Multinodular, PS 0
- Portal Invasion, N1, M1, PS 1-2

Advanced Stage
- Child-Pugh A
- Child-Pugh B

Terminal Stage
- Child-Pugh C
- HVPG <10 or T. Bili <1.5

Assisted Diseases
- RFA/PEI
- Transarterial Chemoembolization
- Sorafenib
- New Agents/ Clinical Trials

Prospective Cohort Study
November 2003 – November 2006
121 patients with HCC
- Consecutive pts referred to Surgical service
- 120 men, 1 woman
- age range 48-88, median 58

Implementation of a multidisciplinary treatment team for hepatocellular cancer at a Veterans Affairs Medical Center improves survival

TAMMY T. CHANG*, RAJIV SAVITNEY*, ALEXANDER MONTO*, BEN DVOREN*, JACOB G. KIRKLAND*, LYDIA STEWART* & CARLOS U. CORVERA*

Improved Outcomes After Development of a Multidisciplinary Treatment Team

- Pts diagnosed at significantly earlier stage, more underwent therapy, and survival was improved compared to the 3 years prior to development of the MDTT

Chang TT et al.
HPB 2008;10:405
Retrospective Analysis of Screening in HCC Pts Referred for Liver Transplant Evaluation

- 269 pts referred to VCU/VA Richmond
- Surveillance grouped:
  - a) standard of care (abd imaging within 1 yr prior to HCC diagnosis), n=172
  - b) substandard surveillance (no imaging, pt with cirrhosis), n=48
  - c) absence (cirrhosis unrecognized), n=59

Transplant: Key Difference in Survival

- 60/269 underwent OLT
- 3-yr survival 81% with OLT vs. 12% without (p<.001)


Quality of Surveillance Determined Survival in Patients Referred for Liver Transplant

- Mean 3-yr survival in all pts who underwent surveillance:
  - standard: 40%
  - substandard: 27%
  - none: 13%
- Recognition of cirrhosis and initiation of surveillance: extremely important


Chemotherapy: Sorafenib (Nexavar®)

- Tyrosine kinase receptor inhibitor
- FDA-approved to treat unresectable HCC
- 400 mg p.o. bid
- Side effects: skin rash (hand/foot), diarrhea, thrombocytopenia
- Precautions: cardiac ischemia, bleeding, hypertension
- Metabolized by the liver, don’t use in CPT B-C
- 10.7 mo. vs. 7.9 mo. median survival (p<0.001) in RCT of 602 pts with advanced HCC, 89% with macroscopic vascular invasion or mets

Llovet JM et al, NEJM 2008;359:378
Is HCC Screening in Cirrhotics Cost Effective?

- By standard criteria, semiannual US is ($30,700/QALY)
- AFP/US or CT strategies exceed $50,000/QALY unless sensitivity and specificity of US decrease to <65% and <60%, respectively
- 58 US: needed to detect 1 small HCC
- $117,247 per small HCC detected; $179,865 per small HCC detected, treated

Summary

- Hepatitis B: importance of therapy, current treatment guidelines
- Hepatitis C, STAT-C agents
- Current management of complications of cirrhosis
- Hepatocellular carcinoma: importance of screening, efficacy of therapies