End stage liver disease, HCC and options for treatment

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USA
Case

• 48 yo female with HCV diagnosed 20 years ago, HIV diagnosed 10 years ago
  – IDU, significant alcohol for 15 years, none now
  – Fatigue, loss of energy on disability
  – PH upper GI bleed

• She heard there are new drugs and wants to be treated
What do you need?

• HCV genotype
• HCV RNA
• Fibrosis stage
Case Labs

- ALT 44; AST 68; bilirubin 2.7; albumin 3.2;
- INR 1.4; AFP 24.4; creatinine 0.8
- WCC 3,000; Hct 45; platelets 82,000
- HCV RNA 607,509 IU/mL
- HCV genotype 1a
- HIV RNA ud, CD4 200
Which statement is **NOT** true?

1. She has cirrhosis
2. She is likely Child’s B
3. She can be treated with all oral DAAs
4. She does not have portal hypertension
5. She needs upper endoscopy
6. She needs HCC screening
ARS Which statement is **NOT** true?

1. She has cirrhosis
2. She is likely Child’s B
3. She can be treated with all oral DAAs
4. She does not have portal hypertension
5. She needs upper endoscopy
6. She needs HCC screening
Diagnosing Cirrhosis – Physical Exam
# Child-Pugh-Turcotte Score = 7

<table>
<thead>
<tr>
<th>Points</th>
<th>1 (normal)</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic encephalopathy</td>
<td>None</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>slight</td>
<td>mod</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>PT or INR</td>
<td>&lt;4 secs $\uparrow$</td>
<td>4-6 secs</td>
<td>&gt;6 secs</td>
</tr>
<tr>
<td>A: 5-6; B: 7-9; C: &gt; 9</td>
<td></td>
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</table>
Model For End Stage Liver Disease

INR  1.4
Bilirubin  2.7  MELD 14
Creatinine  0.8

MELD Formula

The MELD score is calculated using the following formula:

$$\text{MELD Score} = 0.957 \times \log_e(\text{creatinine mg/dL}) + 0.378 \times \log_e(\text{bilirubin mg/dL}) + 1.120 \times \log_e(\text{INR}) + 0.643^1$$

Multiply the score by 10 and round to the nearest whole number.

Laboratory values less than 1.0 are set to 1.0 for the purposes of the MELD score calculation.
Diagnosing Cirrhosis – Labs

EXAM:
Spider nevi, splenomegaly

Most labs not helpful
• 50% Child’s A normal
• AST:ALT often >1

Synthetic dysfunction
• Hypoalbuminemia
• Prolonged PT/INR
• Hyperbilirubinemia

Portal Hypertension
• Thrombocytopenia
• Leukopenia
• Anemia

Renal dysfunction
• Elevated creatinine remember depends on muscle mass

Hyponatremia with ascites
What do you need?

- HCV genotype 1a
- HCV RNA 607,509 IU/mL
- Fibrosis stage cirrhotic
  - Imaging- ultrasound mass in right lobe
  - AFP 22.4
  - EGD Grade 1 varices portal gastropathy
TUMOR MARKERS

• Alpha-fetoprotein (AFP) as a screening test
  - 20-40% with HCC have normal AFP
  - 20-30% without HCC have abnormal AFP
  - The higher the AFP, more likely the diagnosis of HCC

• DCP (PIVKA-II) not better than AFP

• AFP as a prognostic marker
  - predicts overall mortality in HCC
  - predicts prognosis after resection
  - predicts prognosis after liver transplant

1 Marrero JA et al. Gastroenterology 2009;137:110-118
HCC - RADIOLOGIC CHARACTERISTICS QUAD-PHASE CT OF THE ABDOMEN

Arterial Phase Enhancement

Portal Venous phase “washout”
Tumor > 1 cm - One imaging (multi-phase CT/MRI) showing typical HCC characteristics*

* Arterial phase hypervascularity and delayed phase “washout”

Liver biopsy is not necessary for confirming diagnosis, but recommended if imaging criteria not met

HCC – IS BIOPSY NECESSARY?

• Biopsy is not necessary to confirm HCC diagnosis if the lesion meets radiologic criteria in the appropriate clinical setting

• False negative biopsy common in clinical practice and may lead to delay in diagnosis and treatment

• Tumor seeding along the biopsy tract in 1-5%

• Biopsy in selected cases if atypical radiologic appearance or lack of strong risk factor for HCC
Prevalence of HCC in HIV infected veterans: 1996-2009 (n=122)

Ioannou Hepatology 2013: HIV HCV 23 fold higher HCC than HCV alone
HCC risk factors in HIV

• Viral hepatitis
  – lower clearance of AVH, more rapid progression
  – Hepatitis C, Hepatitis B, Hepatitis B and D
• Alcohol –33% prior, 10% currently heavy
• NAFLD estimated to be 30-40% of HIV
• Lower CD4 and older age associated with HCC
• HIV -immune dysregulation causes more inflammation, accelerate hepatic carcinogenesis and weaker anti-tumor response
BCLC STAGING CLASSIFICATION

Stage 0
PST 0, Child-Pugh A
- Very early stage (0)
  - Single < 2 cm, CA in situ
  - Single
  - Portal pressure/ bilirubin
    - Increased
    - No
    - Normal
  - 3 nodules ≤ 3cm

Stage A-C
Okuda 1-2, PST 0-2, Child-Pugh A-B
- Intermediate stage (B)
  - Multinodular, PS 0
  - Associated diseases
  - Increased
  - No
  - Yes

Stage D
Okuda 3, PST >2, Child-Pugh C
- Advanced stage (C)
  - Portal vein invasion, N1,M1, PS 1-2
  - Portal invasion, N1, Mi

Stage 0
- Resection
  - 5-yr survival 50-70%
  - Liver Transplantation
  - PEI/ RFA
  - TACE
  - New agents
  - Symptomatic Tx
    - 1-yr survival 10-20%

Adapted from Llovet JM et al. Lancet 2003;362:1907-17
SURGICAL TREATMENT FOR HCC
CIRRHOSIS AND LIVER FUNCTION

NON-CIRRHOTIC → RESECTION
5% in Western countries
40% in Asia

CIRRHOTIC

Child’s A
Child’s B
Child’s C

→ TRANSPLANT
HEPATIC RESECTION FOR HCC

Predictors of tumor recurrence

• Vascular invasion
• Multi-focal HCC/ satellite tumor nodules
• Tumor size > 5 cm
• Positive resection margins
• Lymph node involvement
• High alpha-fetoprotein > 2000 ng/ml
Survival following resection: Impact of portal hypertension

Survival Distribution Function

- No Portal HTN, normal bilirubin
- Portal HTN, normal bilirubin
- Portal HTN, increased bilirubin

Time (years)

*Llovet et al. Hepatology 1999; 30:1434*
Survival following liver transplantation and surgical resection

Survival Distribution Function

- Liver Transplantation
- Surgical Resection
- No Treatment

Time (years)

LOCAL REGIONAL THERAPIES FOR HCC

CHEMOEMBOLIZATION
Conventional and Drug-eluting beads

ABLATIONS

CHEMICAL
Percutaneous ethanol injection (PEI)

THERMAL
Radiofrequency ablation (RFA)
(Laparoscopic, percutaneous or open)

Microwave/ Cryo- ablation

RADIOEMBOLIZATION (YITTRIUM - 90)
TARGETED THERAPY FOR HCC

Berretta: 27 HIV pts with survival same as HIV neg 12.8mos
Anticancer Drugs 2013
### HCC and HIV survival

<table>
<thead>
<tr>
<th>2 yr survival</th>
<th>HIV +</th>
<th>HIV-</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puoti (R 41)</td>
<td>11%</td>
<td>41%</td>
<td>0.01</td>
</tr>
<tr>
<td>Brau (R 63)</td>
<td>16%</td>
<td>18%</td>
<td>0.6</td>
</tr>
<tr>
<td>Berretta (R 104)</td>
<td>69%</td>
<td>72%</td>
<td>0.048</td>
</tr>
<tr>
<td>Lim (P 23-TB)</td>
<td>44%</td>
<td>60%</td>
<td>0.2</td>
</tr>
</tbody>
</table>

- All note younger age in HIV+ but other factors not common

AIDS 2004; J Hepatol 2007; oncol 2011; JAIDS 2012
HIV HCC outcomes

• 82 HCC/ HIV pts: HCV in 66, HBV in 6, and HBV/HCV in 10.
• HIV/HCV-coinfected patients (6 SVR), HCC incidence increased from 0.2 to 2.8 cases per 1000 person-years between 2000 and 2009.
• 65 deaths median survival 91 d (IQR 31-227d)
  – 3/11 receiving potentially curative therapy died
  – 62/71 ineligible for curative therapy (P = .0001).

Merchante CID 2013-Spain
HIV HCC

• 32% Diagnosed by screening (survival 22 vs 2 mos p <0.0001)
• 70% >5 cm, 29% PVT, 60% multifocal, 16% mets
• 30% within Milan
• 44% AFP >= 200
• Therapy: resection (1), RFA (1), OLT (6), PEI (3), TACE (16), sorafenib (6)
• OLT higher drop out rate in 21 OLT France

Merchante CID 2013; Vibert Hepatol 2011-France
HIV HCV HCC

What options for this lady?
• HIV controlled CD4 200 HIV RNA ud
• HCV cirrhotic
• Child’s B CPT 7, MELD 14
• HCC one lesion
• Portal HTN

How to treat HCC?
Should we treat HCV?
BCLC STAGING CLASSIFICATION

Stage 0
PST 0, Child-Pugh A

Very early stage (0)
Single < 2 cm, CA in situ

Stage A-C
Okuda 1-2, PST 0-2, Child-Pugh A-B

Early stage (A)
Single or 3 nodules < 3 cm, PS 0

Intermediate stage (B)
Multinodular, PS 0

Stage D
Okuda 3, PST >2, Child-Pugh C

Advanced stage (C)
Portal vein invasion, N1,M1, PS 1-2

Terminal stage (D)

Resection
Liver Transplantation
PEI/ RFA
TACE
New agents

Symptomatic Tx
1-yr survival 10-20%

5-yr survival 50-70%
3-yr survival 20-40%

Adapted from Llovet JM et al. Lancet 2003;362:1907-17
HCC and HIV Summary

• Increasing prevalence with longer life span
  – Viral hepatitis, ETOH and NAFLD
• Treating viral hepatitis decreases F4 and HCC but HCC can occur after SVR
• Diagnose cirrhosis- Bx, Fibroscan, APRI, FIB-4
• Imaging of all cirrhotics
• Screening and early diagnosis are critical
• Access to therapies including locoregional therapy and liver transplant