HIV and Hepatocellular Carcinoma

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In theory, there is no difference between theory and practice...

In practice there is...

Chuck Reid
• Case
• Incidence
• Risk factors for HCC
• Screening for HCC
• Treatment Options

Dante’s Inferno/ D Brown!
CASE

- 47 yrs old woman (Hispanic)

1994  HIV diagnosed
1996  HCV diagnosed
1998  CD4 count 342 cells/µl (HAART started)
2004  CD4 count above 400 cells/µl and HIV RNA undetectable

HCV genotype 1a and DNA’d appt s for 3 yrs to co-infection clinic

2003  Peripheral stigmata of cirrhosis (spider naevi, palmar erythema, cryoglobulin associated rash)
US liver- showed splenomegaly
Low platelet count

6- monthly liver ultrasound scans for HCC surveillance
Treatment offered for HCV but patient declined until Jan 2007
CASE

April 2007  non-responder to HCV antiviral therapy, discontinued
Nov 2007   Liver transplant assessment
            MRI Liver  2 HCC  14mm and 27mm in left lobe
            MELD 14 CPB
Jan 2008   Radio-frequency ablation
March 2008 New hepatic mass
July 2008  AFP 56,766 IU/ml
            MRI Liver – multiple hepatic masses and metastases to
            abdominal wall

Palliative care as per patient’s wishes

Sept 2008  Died aged 61 yrs old (at time CD4 count 451cells/µl and
            HIV RNA >75 copies/ml )
Hepatocellular Carcinoma

Patients have two diseases - with independent natural histories

75-90% of all HCCs arise in a cirrhotic liver
All types of cirrhosis may develop HCC
Removal of the cause of cirrhosis doesn’t remove the risk of HCC
Incidence

- Estimated 33 million people infected with HIV worldwide
  Joint UN Programme on HIV/AIDS 2010 Global report

- 50% of HIV patients on HAART do not die of AIDS

- In HIV positive patients 11.9% of non-AIDS defining cancer deaths due to HCC

- In HIV postive patients HCC prevalence rates are 82/10,000 cases (according to data collection on adverse events of anti HIV drugs)

- HCV co-infection strongest predictor of death in US veterans Study
HCC in HIV – Rising Frequency

1995 - 1997 (3 yrs): 2 cases
1998 - 2000 (3 yrs): 21 cases
2001 - 2003 (3 yrs): 36 cases
2004 - 2006 (3 yrs): 46 cases
2006 - 2010 (3.3 yrs): 58 cases

N=168

Kikuchi L et al.,
EASL HCC Symposium,
Dubrovnik, June 2010

Incidence density rate of HCC, cases per 1000 person years

N=82

1999 - 2000: 0.1 cases
2001 - 2002: 0.4 cases
2003 - 2004: 1.0 cases
2005 - 2006: 1.4 cases
2007 - 2008: 2.3 cases
2009 - 2010: 2.1 cases

Merchante N. et al, Clin Infect Dis, Jan-2013
Median survival:

HIV-pos.  5.9 mo
HIV-neg. (Brescia)  17.7 mo
HIV-neg. (CLIP)  18.0 mo

2004 GICAT study 41 cases vs 384 HIV -ve controls
younger, sicker, poor survival, little Rx offered
however 15/41 within Milan!

Puoti M et al., AIDS, Nov-2004
Risk factors for HCC

- Age
- Chronic and occult HBV infection
- Chronic HCV infection
- Diabetes
- Non-alcoholic fatty liver disease
- HIV-1 TAT protein expression
Age and survival of HIV infected patients with HCC

Braü et al. AASLD, Boston 2010, Poster # 1795.
Age and HCC in HIV-Infected Patients

Compared to younger HIV-infected patients with HCC, patients ≥ 50 years

1. are more frequently black
2. tend to have chronic hepatitis C
3. tend to present more frequently with multiple rather than solitary tumors
4. tend to receive effective HCC therapy less often
5. tend toward shorter survival (p= 0.11)

Braü et al. AASLD, Boston 2010, Poster # 1795.
HBV infection

- 5-15 fold increase in risk of HCC in chronic HBV carriers
  
  El-Serag et al. Liver Disease: from bench to bedside-post graduate course, 2004, p159-166

- 6-10% of HIV –infected patients are chronic HBV carriers
  
  Puoti et al. AIDS 2004; 18: 2285-2293

- Occult HBV infection (i.e. Lack of chronic hep B surface antigen but HBV DNA positive) ranges from 10% of HIV patients with anticore IgG ab in ACTG cohort and 89.5% in Swiss cohort
  
HCC incidence in patients with HBV cirrhosis treated with ETV

Long term therapy with TDF decreased incidence of HCC vs predicted risk

- 6-year long-term follow-up from pivotal TDF studies compared with predicted rate of HCC using the REACH-B model
  - Validated in both cirrhotic and non-cirrhotic patients

Kim et al. EASL 2013
Chronic HCV infection

- Rate of fibrosis progression is accelerated in HIV-HCV coinfected patients compared to HCV monoinfection

- HIV-HCV coinfected patients with HCC are younger than those HCV monoinfected
  Sahasrabuddhe et al. Cancer 2012; 118: 6226-33

- Time from HCV infection to HCC is shorter in HIV-HCV coinfected patients
  Sahasrabuddhe et al. Cancer 2012; 118: 6226-33

- Risk of HCC increased 2-fold at CD4+ T cell count of <500 cells/µL and plateaus at <200 cells/µL. Hence immunodeficiency important
  Brau et al. J Hepatol 2007; 47: 527-37
HIV positive patients who received care in the Veterans Affairs (VA) health care system nationally between 1996 and 2009 (n = 24,040 in 2009)

Fig. 1. Trends in the prevalence of (A) cirrhosis, (B) decompensated cirrhosis, (C) HCC, and (D) mortality in HIV-infected veterans during 1996-2009 presented according to HCV status. Solid lines represent actual prevalence. Dotted lines represent prevalence adjusted by direct standardization to the age distribution of the entire population from all calendar years.
Diabetes/ NAFLD

- Insulin resistance common amongst HIV patients

- The HOMA index and age, were independently associated with the risk of HCC occurrence in a prospective cohort of 244 HIV/HCV-co-infected patients with cirrhosis and without treated diabetes.

Salmon et al J Hepatol 2012 Apr;56(4):862-8
HIV and Tat 1

- HIV-1 Tat protein stimulates cell proliferation, inhibits apoptosis, displays angiogenic functions.

- Tat – transgenic mice constitutively express Tat in all tissues. When exposed to a general carcinogen urethane there was significantly more liver tumours in the transgenic mice compared to control mice. *Eur J Cancer 2004 Jan;40(2):275-83*

| Table 1. Incidence of liver and lung lesions in TT and CC mice treated with urethane |
|---------------------------------|---------|----------|---------|----------|----------|----------|
| Liver lesions                  | Animals with lesions | Percentage | Animals with lesions | Percentage | P-value  |
| LCD                            | 19/49   | 39       | 15/159  | 9         | 7.0×10^-6 |
| BLCN                           | 23/49   | 47       | 20/159  | 13        | 1.1×10^-6 |
| HA                             | 12/49   | 24       | 9/159   | 6         | 3.7×10^-3 |
| HC                             | 3/49    | 6        | 0/159   | 0         | 1.2×10^-2 |
| VE                             | 7/49    | 14       | 8/159   | 5         | 3.6×10^-2 |
| HE                             | 15/49   | 31       | 12/159  | 8         | 1.1×10^-4 |
| Lung lesions                   |         |          |         |           |          |
| ACH+LA                         | 8/49    | 16       | 13/159  | 8         | 8.7×10^-2 |
| LC                             | 3/49    | 6        | 6/159   | 4         | 9.3×10^-2 |

TT, tat-transgenic BDF mice; CC, control BDF mice; LCD, liver cell dysplasia; BLCN, basophilic liver cell nodules; HA, hepatocellular adenomas; HC, hepatocellular carcinomas; VE, vascular ectasias; HE, haemangiomas; ACH, alveolar cell hyperplasia; LA, lung adenomas; LC, lung carcinomas. *P* value was obtained by Fisher's exact test.
Prevention of cirrhosis and HCC in HIV infected patients
Screening for HCC

European Guidelines (EACS) recommend in HIV infected patient with HCV related cirrhosis

- 6 monthly liver ultrasound surveillance
- 6 monthly serum alpha-fetoprotein measurement

Rockstroh et al. HIV Med 2008; 9: 82-88
Failure rates in HCC surveillance in general practice

- 2005–2011
- 178 cases of HCC at a single centre
- Retrospective chart review
- Only 20% had some form of surveillance

Surveillance 6x more likely if followed up by hepatologist

Surveillance 7x less likely in alcoholic patients

- Surveyed 20%
- Failure to have surveillance 3%
- Failure to order surveillance 38%
- Failure to recognise liver disease 20%
- Failure to recognise cirrhosis 19%

Requirements of a successful screening test

- Disease sufficiently common
- Disease poses serious risk of morbidity and mortality
- Inexpensive test
- Able to be applied repeatedly
- Minimally invasive
- Minimal risk to screened population
- Population must be accessible and recognizable
- Standardized recall policies
- Effective treatment for those identified with disease
BCLC Staging and Treatment Strategy

- **Very early stage (0)**
  - Single HCC
  - Portal pressure/bilirubin: Increased → Resection
    - Curative treatments (30%) 5-year survival: 50–70%
  - Portal pressure/bilirubin: Normal

- **Early stage (A)**
  - 3 nodules ≤3cm
    - Associated diseases: No → Liver transplantation
      - Curative treatments (50-60%) Median survival untreated: 6-16 months
    - Associated diseases: Yes → PEI/RF

- **Intermediate stage (B)**
  - Associated diseases: No → Resection
    - Curative treatments (30%) 5-year survival: 50–70%
  - Associated diseases: Yes → Chemoembolization
    - RCTs (50-60%) Median survival untreated: 6-16 months

- **Advanced stage (C)**
  - Extrahepatic disease: No → Resection
    - Curative treatments (30%) 5-year survival: 50–70%
  - Extrahepatic disease: Yes → New agents

- **Terminal stage (D)**
  - Symptom control treatment: Survival <3 mo

Adapted from Llovet JM, et al, Lancet 2003;362
## Staging systems for HCC

<table>
<thead>
<tr>
<th>System</th>
<th>Hepatic</th>
<th>AFP</th>
<th>P.S</th>
<th>Tumour burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCLC</td>
<td>CPS</td>
<td>No</td>
<td>Yes</td>
<td>Tumour size, number, PVT</td>
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<tr>
<td>Okuda</td>
<td>Ascites</td>
<td>No</td>
<td>No</td>
<td>Tumour size, number, metastases, PVT</td>
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<tr>
<td>Okuda</td>
<td>Albumin</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Okuda</td>
<td>Bilirubin</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>TNM</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Tumour size, number, metastases, PVT</td>
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<tr>
<td>CLIP</td>
<td>CPS</td>
<td>Yes</td>
<td>No</td>
<td>Tumour &gt; 50% of liver, number, PVT</td>
</tr>
<tr>
<td>CUPI</td>
<td>Ascites</td>
<td>Yes</td>
<td>Symptoms</td>
<td>TNM</td>
</tr>
<tr>
<td>CUPI</td>
<td>Bilirubin</td>
<td>Yes</td>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>CUPI</td>
<td>AP</td>
<td>Yes</td>
<td>Symptoms</td>
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</tr>
<tr>
<td>JIS</td>
<td>CPS</td>
<td>No</td>
<td>No</td>
<td>TNM</td>
</tr>
<tr>
<td>GETCH</td>
<td>Bilirubin</td>
<td>Yes</td>
<td>Yes</td>
<td>PVT</td>
</tr>
</tbody>
</table>
Treatment

- Local ablative therapy
- Surgical resection
- Chemotherapy
- Transplantation

TACE + RFA

Pre-Rx

Post- TACE

Post- TACE + RFA at 33 month
Challenges in the Development of Drug Therapy for HCC

- Advanced stage at presentation
- Relative resistance to cytotoxic chemotherapy
- Liver dysfunction
  - Poor drug metabolism
  - Altered plasma-binding proteins
  - Altered drug distribution volumes
  - Competing cause of morbidity and mortality
- Diverse underlying etiologies of liver dysfunction among patients
- Difficulty in quantifying tumor response
- Multiple staging systems

Giglia et al, Cancer Control 2010;17:120-9
# Levels of Evidence in the Assessment of Benefits in the Treatment of “Advanced” HCC

<table>
<thead>
<tr>
<th>Systemic treatment</th>
<th>Benefit</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>Increased survival</td>
<td>1iA</td>
</tr>
<tr>
<td>Hormonal compounds</td>
<td>No survival benefit</td>
<td>1iA</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td></td>
<td></td>
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<tr>
<td>Antiandrogen</td>
<td></td>
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<tr>
<td>Seocalcitiol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic chemotherapy</td>
<td>No survival benefit</td>
<td>1iiA</td>
</tr>
<tr>
<td>Interferon</td>
<td>No survival benefit</td>
<td>1iiA</td>
</tr>
</tbody>
</table>

Carcinoma in liver

Chemo-embolization mixture administered to carcinoma through catheter

Hepatic artery

Catheter enters through skin into femoral artery

Aorta

A

A' Carcinoma

A' Hepatic artery

A' Catheter

B

x-ray
Transplantation

Multicenter Italian Experience in Liver Transplantation for Hepatocellular Carcinoma in HIV-Infected Patients. Multicenter study (3 Italian transplant centers in northern Italy)

30 HIV-positive patients affected by HCC who underwent LT with 125 HIV-uninfected patients who received the same treatment from September 2004 to June 2009.

RESULTS: HIV-infected patients were younger, they were more frequently anti-HCV positive, and a higher number of HIV-infected patients presented a coinfection HBV-HCV. Pre-LT treatments (liver resection and or locoregional treatments) were similar between the two groups. Histological characteristics of the tumor were similar in patients with and without HIV infection. No differences were observed in terms of overall survival and HCC recurrence rates.

CONCLUSION: LT for HCC is a feasible procedure and the presence of HIV does not particularly affect the post-LT outcome.
HCC: ‘the greatest obstacle to knowledge is not ignorance it is the illusion of knowledge’

Key messages

- Increasing recognition of liver as a cause of disease ‘burden’: thus screening/ investigation critical
- Co-ordination of HIV/ surgery/ hepatology/ oncology/ palliative medicine
- Rapidly improving sophistication of cross-sectional imaging
- Evidence strength equivocal - urgent need for better trials
- Role of transplantation and surgery
- Heterogeneity in imaging/ treatment modalities
- Selection of patient critical
- Concept of field change - tumour biology: Individualised therapy
Molecular classification of HCC
Genomic profiling from the tumor

<table>
<thead>
<tr>
<th>S1</th>
<th>S2</th>
<th>S3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGF-β</td>
<td>MYC</td>
<td>Retained hepatocyte-like phenotype</td>
</tr>
<tr>
<td>WNT ↑</td>
<td>AKT ↑</td>
<td></td>
</tr>
<tr>
<td>E2F1 ↑, p53 ↓</td>
<td>IFN ↓</td>
<td></td>
</tr>
</tbody>
</table>

Published subclasses:
- Poor survival
- Proliferation
- Late TGF-β
- EpCAM (+)
- Good survival
- CTNNB1

Clinical phenotype:
- High-grade
- Larger tumor
- Invasive
- Low-grade
- Smaller tumor
- AFP ↑

Villanueva A et al. Gastroenterology 2008
Molecular classification of HCC
Prognostic Gene Signatures from adjacent liver

Gene Signature from cirrhotic tissue
(n=186 genes)

HCC development
(HCV-cirrhosis, n=216)

Survival
(Resected patients, n=225)

Final thought

‘knowing is not enough, we must apply willing is not enough we must do…’

Johann Wolfgang von Goethe (1749-1832)