The impact of the treatment of HCV in developing Hepatocellular Carcinoma

> Paul Y Kwo, MD **Professor of Medicine** Medical Director, Liver Transplantation Gastroenterology/Hepatology Division Indiana University School of Medicine 975 W. Walnut, IB 327 Indianapolis, IN 46202-5121 phone 317-274-3090 fax 317-274-3106 email pkwo@iu.edu

Hepatocellular Carcinoma (HCC)

- •Hepatocellular carcinoma is the 4th most common cancer in the world
- Third leading cause of cancer related death
- 80% of HCC is caused by chronic HCV or HBV infection
- HCC rarely seen during the first 4 decades of life, -except in populations in which HBV infection is hyperendemic.
- •The mean ages of diagnosis with HCC were :
 - -55-59 years in China
 - -63-65 years in Europe and North America

HCC and Hepatitis C

- Risk of HCC increases with fibrosis stage
- Most cases of HCV-related HCC occur among patients with advanced fibrosis/cirrhosis
- Incidence of cirrhosis 25–30 years after HCV infection is 15%-35%,
 - highest among recipients of HCV-contaminated blood products and hemophiliac patients
 - lowest among women who received dose of contaminated anti-D immunoglobulin
- HCC develops at annual rate of 1%–4%
 - rates up to 8% have been reported in Japan.

HCC and Hepatitis C: Other reported risk factors

- Gender
- Co-infection with HBV or HIV
- Diabetes, obesity, steatosis
- viral genotype (HCV 1b)
- Level of alcohol consumption
- Age
- Thrombocytopenia
- Increased levels of alpha -fetoprotein

Age-standardized incidence rates of liver cancer per 100,000 person-years



Prevalence of HBsAg carrier and chronic HCV status in different geographic regions



Multistep Malignant Transformation to HCC

HCC²

Epigenetic alterations Genetic alterations

Dysplastic nodules¹

Liver cirrhosis

Hepatitis C Hepatitis B Ethanol NASH Normal liver

| Potential Therapeutic Targets | | | | | | | |
|--------------------------------------|------------------------|-------------------|--|--|--|--|--|
| Oxidative stress and inflammation | Viral oncogenes | Carcinogens | | | | | |
| Growth factors | Telomere shortening | Cancer stem cells | | | | | |
| Loss of cell cycle checkpoints | Anti-apoptosis | Angiogenesis | | | | | |

Tornillo L, et al. Lab Invest. 2002;82:547-553.
 Verslype C, et al. AASLD 2007. Abstract 24.

Is Hepatitis C infection carcinogenic?

- Active HCV infection increases the risk of HCC by 18-fold
- 8% of HCC cases in HALT-C study had no cirrhosis
- Hepatitis C elicits inflammatory and fibrotic responses in the host contributing to carcinogenesis
- SVR reduces risk of HCC by 3 fold in cirrhotic patients



Cirrhosis regression in patients with and without a sustained viral response in trials in which the follow-up biopsy had a mean or median time of < 36-months



Test for Heterogeneity: Chi² = 2.07 (P = 0.35), I² = 3%

Test for overall effect: Z = 3.47 (P < 0.01)

Liver Int. 2015; 35: 30-36

Cirrhosis regression in patients with and without a sustained viral response in trials in which the followup biopsy had a mean or median time of >36-months



Test for Heterogeneity: Chi² = 9.95 (P < 0.01), I² = 80%

Test for overall effect: Z = 2.10 (P = 0.04)

Liver Int. 2015; 35: 30-36

Antiviral Therapy With SVR Reduces Risk of Hepatocellular Carcinoma in Patients With Hepatitis C Virus–Related Cirrhosis

| SVR NSV | | R | | Risk ratio | Risk ratio | | | | |
|--|---------------|----------|-----------|------------|------------|---------------------|---------------------|--|--|
| Study or subgroup | Events | Total | Events | Total | Weight | M-H, random, 95% CI | M-H, random, 95% Cl | | |
| Azzaroli 2004 | 0 | 21 | 2 | 50 | 1.0% | 0.46 [0.02, 9.27] | | | |
| Braks 2007 | 1 | 37 | 24 | 76 | 2.3% | 0.09 [0.01, 0.61] | | | |
| Bruno 2007 (1) | 7 | 124 | 122 | 759 | 16.0% | 0.35 [0.17, 0.73] | | | |
| Floreani 2008 (2) | 0 | 40 | 5 | 38 | 1.1% | 0.09 [0.00, 1.51] | ← | | |
| Hasegawa 2007 (3) | 3 | 48 | 16 | 57 | 6.3% | 0.22 [0.07, 0.72] | | | |
| Hung 2006 | 5 | 73 | 11 | 59 | 8.7% | 0.37 [0.14, 1.00] | | | |
| Nishiguchi 1995 | 0 | 7 | 2 | 38 | 1.0% | 0.97 [0.05, 18.43] | | | |
| Okanoue 1999 | 0 | 2 | 7 | 38 | 1.3% | 0.87 [0.06, 11.79] | | | |
| Shioda 1999 | 4 | 204 | 18 | 448 | 7.6% | 0.49 [0.17, 1.42] | | | |
| Shiratori 2005 | 11 | 64 | 73 | 207 | 26.9% | 0.49 [0.28, 0.86] | | | |
| Tanaka 1998 | 0 | 8 | 10 | 47 | 1.2% | 0.25 [0.02, 3.96] | | | |
| Veldt 2008 | 3 | 142 | 32 | 337 | 6.4% | 0.22 [0.07, 0.71] | | | |
| Yoshida 1999 (4) | 1 | 53 | 30 | 168 | 2.2% | 0.11 [0.01, 0.76] | | | |
| Yu 2006 | 9 | 85 | 27 | 80 | 18.3% | 0.31 [0.16, 0.63] | | | |
| Total (95% CI) | | 908 | | 2402 | | 0.35 [0.26, 0.46] | • | | |
| Heterogeneity: Test for overall effect: 7 = | $Chi^2 = 8.0$ | 67, df = | = 13 (P = | .80) | | | 0.02 0.1 1 10 50 | | |

Maintenance interferon did not reduce risk of HCC

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2010;8:192–199

SVR reduces HCC risk across all fibrosis stages

| Study | | | RR (95% CI) | Weight (%) |
|--|------------|---------------|--------------------|------------|
| | Favors SVR | Favors no SVR | | |
| Arase 2007 [10] | | | 0.16 (0.04, 0.67) | 16.83 |
| Coverdale 2004 [11] | - | | 0.18 (0.03, 1.34) | 11.22 |
| Giannini 2001 [12] | | | 0.46 (0.02, 11.13) | 5.42 |
| Kasahara 2004 [15] | ••••• | | 0.04 (0.01, 0.28) | 11.33 |
| Lau 1998 [18] | | | 0.33 (0.01, 8.01) | 5.41 |
| Yoshida 2004 [27] | - | | 0.19 (0.09, 0.42) | 26.88 |
| Yu 2006 [28] | - | - | 0.80 (0.29, 2.19) | 22.90 |
| Overall (I-squared = 45.2%, P = .090) | \Diamond | | 0.23 (0.10, 0.52) | 100.00 |

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2010;8:280 – 288

SVR reduces HCC risk in those with cirrhosis



CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2010;8:280 – 288

SVR Decreases but Does Not Eliminate Risk for Liver Related Complications in those with hepatitis C



| No. at risk | | | | | | | | | | | |
|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Without SVR | 405 | 393 | 382 | 363 | 344 | 317 | 295 | 250 | 207 | 164 | 135 |
| With SVR | 192 | 181 | 168 | 162 | 155 | 144 | 125 | 88 | 56 | 40 | 28 |



No. at risk Without SVR 405 390 375 349 326 294 269 229 191 151 122

Van der Meer, et al. JAMA 2012:308:2584-2593.



| No. at risk | | | | | | | | | | | |
|-------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Without SVR | 405 | 392 | 380 | 358 | 334 | 305 | 277 | 229 | 187 | 146 | 119 |
| With SVR | 192 | 181 | 168 | 162 | 155 | 144 | 125 | 88 | 56 | 40 | 28 |



314

288 259 216

361

337

143 113

184

No. at risk Without SVR 405 384

Projected Incidence of HCV Related Liver Cancer and Death Also Expected to Peak in Coming



DCC=decompensated cirrhosis; HCC=hepatocellular carcinoma

Between 1995 and 2010, 41% of the 126,862 new primary registrants for liver transplants carried a diagnosis of HCV infection²

HCV and HCC | 16 1. Rein DB, et al. *Dig Liver Dis*. 2011;43(1):66-72. **2.** Biggins SW, et al. *Liver Transpl*. 2012;18(12):1471-1478.

AASLD Surveillance Guidelines

- Surveillance recommended in at-risk groups
- HCC surveillance should be performed with ultrasound
- Patients should be screened at 6-mo intervals
 - AFP levels not part of surveillance guidelines

APASL Surveillance Guidelines

Surveillance recommended in at-risk groups
HCC surveillance should be performed with ultrasound
Patients should be screened at 6-mo intervals

AFP levels are part of surveillance guidelines

Bruix J, et al. AASLD HCC guidelines. July 2010. APASL Guidelines Hepatol Int (2010) 4:439–474



Genotype 3 requires additional strategies to achieve success of genotype 1

TURQUOISE II: 12 vs 24 Wks OMV/PTV/RTV + DSV + RBV in



Poordad F, et al. EASL 2014. Abstract O163. Poordad F, et al al. N Engl J Med. 2014;370:1973-1982.

SOLAR: SVR12 in Patients With Advanced Liver Disease



Daclatasvir/Asunaprevir/Beclabuvir, ± Ribavirin for 12 weeks for G1



^aOne patient with HCV RNA <LLOQ TND at end of therapy and posttreatment Week 4 had missing data at posttreatment Week 12.

Error bars indicate 97.5% confidence intervals.

Groups in Whom the Rik of HCC is Increased, but in Whom Efficacy of Surveillance Has Not Been Demonstrated

| Population Group | Threshold Incidence for Efficacy of Surveillance (%/year) | Incidence of HCC (%/year) |
|---|--|------------------------------|
| Hepatitis B Carriers <40 (males) or 50 (females) | 0.2 | <0.2 |
| | | |
| Hepatitis C and stage 3 fibrosis | 1.5 | <1.5 |
| Noncirinotic NAFLD | 1.5 | 1 |

The Impact of HCV Treatments on HCC development

- We have the tools to achieve SVR in the majority of chronically infected hepatitis C patients
- These tools can reduce HCC development worldwide
- High SVR rates in F0-F4 fibrosis
- Those who are cured with cirrhosis must be entered into screening for HCC (US+AFP) if available
- Cirrhosis regression will occur in many who achieve SVR
- HCC risk will fall
 - Long term studies required to assess natural history of cirrhosis patients who achieve SVR on HCC development

The Impact of HCV Treatments on HCC development

d



Journal of Viral Hepatitis, 2015, 22, (Suppl. S1), 1–5