LA TERAPIA DELL’EPATOCARCINOMA OGGI

Giuseppe Cabibbo
& Liver Unit, PROMISE
University of Palermo, Italy
giuseppe.cabibbo78@gmail.com
Key Aspects of the Presentation

- Clinically actionable evidence
- New developments in the field (avoid spending much time on well-known information)
- Anticipated future directions
- Controversial aspects
- Areas of difficulty in management
Hepatocellular carcinoma (HCC): Introduction

high rate of mortality;

strictly associated with chronic liver disease, mainly cirrhosis;

well-known risk factors. Dominant role of HBV and HCV; rising role of NASH, obesity; and diabetes;

biological and clinical heterogeneity and wide prognosis.
Meta-analysis of aggregate data (MA-AD): HCV-untreated arms of studies after curative treatments

Pooled Actuarial Recurrence Rate
- 6 months: 7.4% (Range: 0-12.5%)
- 24 months: 47% (Range: 32-100%)

Pooled Survival Recurrence Rate
- 3 years: 80% (Range: 65.3-95%)
- 5 years: 59% (Range: 47-78%)

Range at 24months: 32-100%
Range at 5yr: 47-78%
Application of the Intermediate-Stage Subclassification to Patients With Untreated Hepatocellular Carcinoma

Edoardo G. Giannini, MD, PhD, FACG, Alessandro Moscatelli, MD, Gaia Pellegatta, MD, Alessandro Vitale, MD, Fabio Farinati, MD, Francesca Ciccarese, MD, Fabio Piscaglia, MD, Gian Lodovico Rapaccini, MD, Maria Di Marco, MD, Eugenio Caturelli, MD, Marco Zoli, MD, Franco Borzio, MD, Giuseppe Cabibbo, MD, Martina Felder, MD, Rodolfo Sacco, MD, Filomena Morisco, MD, Gabriele Missale, MD, Francesco Giuseppe Foschi, MD, Antonio Gasbarrini, MD, Gianluca Svegliati Baroni, MD, Roberto Virdone, MD, Alberto Masotto, Franco Trevisani, MD and for the Italian Liver Cancer (ITA.LI.CA) Group

9 untreated HCC patients

![Diagram showing survival probability over time for untreated HCC patients with stages B4, B3, B2, and B1.

**Am J Gastroenterol** 2020
A Meta-Analysis of Survival Rates of Untreated Patients in Randomized Clinical Trials of Hepatocellular Carcinoma

Giuseppe Cabibbo,¹,4 Marco Enea,² Massimo Attanasio,² Jordi Bruix,³ Antonio Craxi,¹ and Calogero Cammà¹,5

Untreated control groups of 30 RCTs

1-year survival rate

17.5%

p for heterogeneity < 0.0001

2-year survival rate

7.3%

Range 0 – 75%

Range 0 – 50%

Cabibbo et al. Hepatology
## The Barcelona Clinic Liver Cancer (BCLC) Staging Classification for HCC

<table>
<thead>
<tr>
<th>BCLC stage</th>
<th>Performance status</th>
<th>Tumor volume, number and invasiveness</th>
<th>Child-Pugh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very early</td>
<td>0</td>
<td>Single &lt; 2 cm</td>
<td>A</td>
</tr>
<tr>
<td>Early</td>
<td>0</td>
<td>Single or 3 nodules &lt; 3 cm</td>
<td>A – B</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0</td>
<td>Large/Multinodular</td>
<td>A – B</td>
</tr>
<tr>
<td>Advanced</td>
<td>1 – 2</td>
<td>Portal invasion and/or Extrahepatic spread N1M1</td>
<td>A – B</td>
</tr>
<tr>
<td>Terminal</td>
<td>&gt; 2</td>
<td>Any of above</td>
<td>C</td>
</tr>
</tbody>
</table>

Il grande assente...
Hepatic decompensation is the major driver of death in HCV-infected cirrhotic patients with successfully treated early hepatocellular carcinoma

HCC patients in ITA.LI.CA. database since 2007
N = 3309

Inclusion criteria:
- HCV-related early and very early HCC
- No-SVR
- Complete response after hepatic resection or thermal ablation
- 1456 HCC patients with aetiology other than HCV
- 797 patients with HCV-related no-early HCC
- 603 patients with HCV-related untreated HCC
- 182 patients with HCV-related treated early HCC and without complete response after resection or thermal ablation
- 43 patients with SVR by PegIFN and ribavirin achieved before HCC diagnosis

N = 371

Patients eligible for the study
N = 328

Time dependent Cox model (MV analysis)

<table>
<thead>
<tr>
<th>Predictor of Survival</th>
<th>HR</th>
<th>95%CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early recurrence</td>
<td>2.5</td>
<td>1.2-5.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Early hepatic decompensation</td>
<td>7.5</td>
<td>4.2-13.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Direct antiviral agents after successfully treated early HCC improve survival in HCV-cirrhotic patients

Improvement in overall survival seems due to significant reduction in hepatic decompensation

Cabibbo G. et al, on behalf RESIST-HCV & ITA.LI.CA. J Hep
Predictors of Survival of Patients with Advanced HCC Who Permanently Discontinued Sorafenib

Conclusions:
1) The survival following sorafenib discontinuation is significantly influenced by reason for drug withdrawal, i.e. adverse effects, liver impairment and tumour progression pattern.

2) In patients eligible to 2nd line trials, survival is determined by reason of sorafenib discontinuation, performance status and extrahepatic tumor burden.

3) In real life practice, these results are keys in prognostic prediction and design/analysis of second line trials.
Surgical Resection

Optimal candidates:

- BCLC stage 0 or A
  - Child-Pugh A
  - Performance status 0
  - Single tumors
  - Normal portal pressure
  - Normal bilirubin
- Excellent functional reserve

5-year survival 60-70%

High recurrence rate
- 50% at 3 years
- 70% at 5 years

Too restrictive in real life: > 50% are above….

### Ablation Therapies

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Minimally invasive, easily repeatable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disadvantage</td>
<td>Higher recurrence risk with respect to resection</td>
</tr>
</tbody>
</table>

- Radiofrequency ablation (RFA); MW ablation
- Percutaneous ethanol injection (PEI)

**Ideal candidates:**
- BCLC Stage A disease (No vascular invasion or metastases)
- Child-Pugh A or B
- **Single nodule < 2 cm** (feasible also for solitary tumor < 5 cm or ≤ 3 nodules < 3 cm)

**RFA or PEI**
- Year survival 40-50%

**High recurrence rate**
- 50% at 3 years
- 70% at 5 years

References:
- Bruix J, Sherman M. Hepatology 2005; 42: 1208-1236;
Tutti i pazienti con HCC singolo e funzione epatica preservata vanno considerati per un trattamento curativo (chirurgia o ablazione), scegliendolo in base alle dimensioni della lesione:

- **HCC ≤2 cm**: se approcciabile in sicurezza con trattamenti interstiziali percutanei o laparoscopici, la termoablazione va considerata il trattamento di prima linea, se eseguita in centri esperti.

- **HCC di 2.1–3 cm**: la scelta tra chirurgia e termoablazione deve essere fatta caso per caso e multidisciplinarmente, anche se la resezione (anatomica) è il trattamento preferibile per radicalità.

- **HCC >3 cm**: la resezione epatica è il trattamento di prima scelta.
Relevance of tumor location

RFA  Resection  TACE
Liver Transplantation

Advantage
- Removal of the diseased liver together with the tumor

Disadvantage
- Long waiting lists

Optimal candidates:
- BCLC Stage A disease
- No vascular invasion
- No metastases
- Fulfill the Milan criteria
  - Solitary tumor < 5 cm or
  - ≤ 3 nodules < 3 cm

5-year survival 70% Recurrence rate < 15%

... but organ shortage and too strict criteria (UCSF, up-to-seven AFP, ...)

Trapianto

Considerazione organizzativa generale

Per **tutti** i pazienti in età trapiantologica e ad alto potenziale di beneficio da trapianto, la strategia terapeutica dovrebbe essere **condivisa precocemente** (anche in rete) con un **centro trapianti**, al fine di ottimizzare l’iter terapeutico.
Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma: Meta-Analysis of Randomized Controlled Trials

Systematic Review of Randomized Trials for Unresectable Hepatocellular Carcinoma: Chemoembolization Improves Survival

Josep M. Llovet and Jordi Bruix for the Barcelona-Clinic Liver Cancer Group

A

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin</td>
<td>Gastroenterology</td>
<td>1998</td>
<td>63</td>
</tr>
<tr>
<td>GETCH</td>
<td>NEJM</td>
<td>1995</td>
<td>96</td>
</tr>
<tr>
<td>Bruix</td>
<td>Hepatology</td>
<td>1998</td>
<td>80</td>
</tr>
<tr>
<td>Pallister</td>
<td>J Hepatol</td>
<td>1998</td>
<td>73</td>
</tr>
<tr>
<td>Lo</td>
<td>Hepatology</td>
<td>2002</td>
<td>78</td>
</tr>
<tr>
<td>Llovet</td>
<td>Lancet</td>
<td>2002</td>
<td>112</td>
</tr>
<tr>
<td>OVERALL</td>
<td></td>
<td></td>
<td>503</td>
</tr>
</tbody>
</table>

Random effects model (DerSimonian & Laird), OR (95% CI)

Favors treatment Favors control

Heterogeneity: Q=7.73, P=0.14
HCC BRIDGE study
18,031 pts (67% from Asia, 20% from Europe and 13% from North America)

First Recorded HCC Treatment by BCLC Stage

- Transplant
- Resection
- RFA/PEI
- Other locoregional therapy\(^c\)
- Other systemic therapy\(^b\)
- Sorafenib
- Radiotherapy
- TACE
- Palliative care

\(\text{a} \quad \text{Percentages are based on number of patients with data available; total may add up to } >100\% \text{ if more than one treatment was started concurrently.}\)
\(\text{b} \quad \text{Any systemic therapy other than sorafenib (e.g., doxorubicin, gemcitabine, cisplatin, or other cytotoxic or biological agent).}\)
\(\text{c} \quad \text{Any locoregional therapy not clearly RFA/PEI or TACE (e.g., TARE or cryoablation).}\)
Curative therapies are superior to standard of care (TACE) for intermediate stage hepatocellular carcinoma

Survival by treatment of 456 BCLC-B patients

Treatment choice was an independent prognostic factor for BCLC B pts after adjustment for other predictors.

TACE-RFA was superior to RFA alone in improving survival for patients with HCC less than 7 cm.
Radioembolizzazione (TARE)

È una brachiterapia (isotopo β-emittente Itrio$^{90}$) nella quale la sorgente radioattiva viene inserita nella rete vascolare tumorale.

È costosa, complessa e con potenziale elevata tossicità epatica, gastro-duodenale e polmonare. Pertanto, dovrebbe essere praticata solo nei centri di riferimento per le malattie neoplastiche epatiche e con una grande esperienza in merito.

Data che le microsfere hanno un effetto embolizzante minimo, può essere effettuata in sicurezza anche nel paziente con trombosi portale (tronco e rami intraepatici).
TARE: (potenziali) Indicazioni

- Pazienti con controindicazioni alla TACE (trombosi portale);
- Pazienti già trattati con TACE, senza risposta completa;
- Pazienti con tumori di grandi dimensioni, con pattern infiltrante, tumori ipovascolari;
- Pazienti intolleranti al sorafenib;
- Down-staging (pre-OLT) e terapia “ponte” per il trapianto
TARE: open issues

Significativo vantaggio nel disease control rate vs sorafenib (RCT) (1,2); Significativo vantaggio in Time to Progression vs TACE (RCT)(3).

Contrasto

Non evidenza di guadagno di sopravvivenza in RCTs:

- vs TACE nel paziente intermedio (3); vs sorafenib nel paziente avanzato (1,2).
- Pochi dati sulla safety con adeguato follow-up.

EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma 2018

Prognostic stage

Very early stage (0)
- Single < 2 cm
- Preserved liver function
- PS 0

Early stage (A)
- Single or 2-3 nodules < 3 cm
- Preserved liver function
- PS 0

Intermediate stage (B)
- Multinodular, unresectable
- Preserved liver function
- PS 0

Advanced stage (C)
- Portal invasion/extrahepatic spread
- Preserved liver function
- PS 1-2

Terminal stage (D)
- Not transplantable HCC
- End-stage liver function
- PS 3-4

HCC in cirrhotic liver

Solitary

2-3 nodules ≤ 3 cm

Optimal surgical candidate

Yes

No

Transplant candidate

Treatment

Ablation

Resection

Transplant

Ablation

Chemoembolization

Systemic therapy

BSC

Survival

> 5 years

First-line

Sorafenib

Lenvatinib

Second-line

Regorafenib

Cabozantinib

Ramucirumab

European Association for the Study of the Liver, J Hepatol 2018
Sorafenib improved overall survival in HCC patients

<table>
<thead>
<tr>
<th></th>
<th>SHARP</th>
<th>Asia–Pacific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, sorafenib</td>
<td>10.7 months</td>
<td>6.5 months</td>
</tr>
<tr>
<td>Median, placebo</td>
<td>7.9 months</td>
<td>4.2 months</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.69 (0.55–0.87)</td>
<td>0.68 (0.50–0.93)</td>
</tr>
</tbody>
</table>

Survival according to sorafenib dose

- Confirmed by MV analysis

SOFIA study*

- All pts started at full dose
- Prospective study

RDS, reduced starting dose
SDS, Standard starting dose

- Retrospective Study
- Propensity score matching

Iavarone, Cabibbo et al. Hepatology 2011

Reiss K, et al. JCO 2017
Ten Years Later

First line systemic therapy (positive phase III trial)

- Sorafenib (2008)
- Lenvatinib (2018)

- nivolumab (?)

Second line systemic therapy (positive phase III trial)

- Regorafenib (2017)
- Cabozantinib (2018)
- Ramucirumab (2019)

- nivolumab (?)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>RAF/MEK/ERK pathway VEGFR/PDGFR</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>VEGFR</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>VEGF1/VEGF2/VEGF3/ PDGFR/FGFR/KIT/RET/RAF-1/ B</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>MET/VEGFR2/FLT3/KIT/ RET</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>VEGFR2</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
</tr>
</tbody>
</table>
Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial

Kudo M. et al. Lancet 2018

- Non-inferiority trial
- No patients with > 50% liver occupation, bile duct occupation, or invasion of the main portal vein
Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): randomised, double-blind, placebo-controlled, phase 3 trial

Bruix J et al. Lancet 2017

Randomization 2:1

OS: 10.6 mos vs 7.8 mos

- Sorafenib intolerant patients non included in the study.
Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma

- Approximately 30% of patients received 2 prior systemic regimens.

Abou-Alfa G.K. et al. NEJM 2018
Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ramucirumab (n = 197)</th>
<th>Placebo (n = 95)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mos</td>
<td>8.5</td>
<td>7.3</td>
<td>0.71 (0.531-0.949)</td>
</tr>
<tr>
<td>P</td>
<td>.0199</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-mo survival, %</td>
<td>36.8</td>
<td>30.3</td>
<td>0.2930</td>
</tr>
<tr>
<td>18-mo survival, %</td>
<td>24.5</td>
<td>11.3</td>
<td>0.0187</td>
</tr>
</tbody>
</table>

Randomization 2:1

Patients at Risk, n

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td>197</td>
<td>172</td>
<td>121</td>
<td>87</td>
<td>56</td>
<td>37</td>
<td>26</td>
<td>14</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>95</td>
<td>76</td>
<td>50</td>
<td>36</td>
<td>19</td>
<td>12</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

baseline AFP ≥ 400 ng/mL
Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial.

The target population was enriched by recruiting patients with increased alpha-fetoprotein (AFP) ≥ 400 ng/mL so that is the first positive phase III study conducted in a biomarker-selected population.

Which (and how) HCC patients can be treated after sorafenib?

Patients with advanced HCC prior treated with sorafenib, with good liver function

- **Regorafenib**
  Progressor but tolerant to sorafenib

- **Cabozantinib**
  Progressor and/or intolerant to sorafenib

- **Ramucirumab**
  Progressor and/or intolerant to Sorafenib with AFP > 400

Direct comparisons are not feasible.
Sequential Therapy for HCC

Kudo M. Liver Cancer
Patients should be discussed in multidisciplinary teams to fully capture and tailor individualised treatment options (evidence low; recommendation strong).

Multidisciplinary Approach to HCC

The management of HCC encompasses multiple disciplines that includes hepatologists, diagnostic radiologists, pathologists, transplant surgeons, surgical oncologists, interventional radiologists, medical oncologists, radiation oncologists, nurses, and palliative care professionals. A recent study showed that the development of a true multidisciplinary clinic with a dedicated tumor board review for HCC patients increased survival. Therefore, HCC patients should be seen in these clinics whenever it is feasible, and, if not, a referral to a center with a true multidisciplinary clinic should be considered.
I pazienti con HCC dovrebbero essere riferiti ad un **Team Multidisciplinare** che dovrebbe includere:

- epatologo
- oncologo
- radiologo (diagnostico e interventista)
- chirurgo specializzato in patologia del fegato
- anatomo-patologo

... e dovrebbero avere un ruolo attivo nella cura di questi pazienti.