10 Years of Clinical Trials

Review of the past and current clinical trials with a particular eye on the comparison between locoregional therapy (LRT) approaches and in combination with medical treatments.

Todd Schlachter MD
Disclosures

- **Support:**
  - NCI RO1, Guerbet,
Locoregional and medical therapy for HCC

- cTACE vs DEB-TACE
- DEB-TACE vs TAE
- Y90 in PVT
- Y90 vs cTACE
- Y90 vs sorafenib

- Ablation/TACE plus Check-point inhibitor
- TACE plus sorafenib
- Y90 plus sorafenib

- TACE Protocol
- DEB/cTACE/TAE

- Radioembolisation

- Blood biomarker

- Tissue biomarker

- Modality
  - RFA/Cryo/TACE, HIFU/IRE

- Immune modulator
  - Effector/inhibitor cells/cytokines

- TKIs & c-met
  - sorafenib/lenvatinib/regorafenib/cabozantinib

- Schedule
  - Before/after/sequential/interrupted/continuous
Differences in IA-Locoregional therapy for HCC

- cTACE vs DEB-TACE
- DEB-TACE vs TAE

IA=IntraArterial

- Tissue biomarker
- Prediction, response

- Blood biomarker
- Immune modulator
  - Effector/inhibitor cells/cytokines

- TKIs & c-met
  - sorafenib/lenvatinib/regorafenib/cabozantinib

- Schedule
  - Before/after/simultaneous
    - Sequential/interrupted/continuous

- TACE Protocol
  - DEB/cTACE/TAE

- Radioembolisation

DOI: https://doi.org/10.1016/j.jhep.2019.01.027
cTACE versus DEB-TACE versus TAE

- **Precision V phase II 2010 DEB-TACE vs cTACE**
  - 212 patients; Early, intermediate and advanced disease patients
  - Drug eluding bead (DEB) group better response however not statistically significant.
  - In advanced disease DEB-TACE showed significant increase in objective response
  - DEB-TACE was associated with improved tolerability and reduction in serious liver toxicity and reduction in doxorubicin related to side effects

- **K. Brown MSKCC 2016 TAE vs DEB-TACE**
  - Prospective Single center, single-blind, randomized phase 2 trial
  - 101 patients; Early, intermediate and advanced disease patients
  - No significant difference between DEB versus TAE alone;
    - overall survival approximately 21 months in both groups
Differences in IA-Locoregional therapy for HCC

- cTACE vs DEB-TACE
- DEB-TACE vs TAE

**Take Home**

- No survival differences b/t techniques, in this heterogeneous BCLC-B/C population.
- Subgroups may benefit from one or the other techniques.
- QOL, post-op embolization and side-affects are different based on technique.
Radioembolization as locoregional therapy for HCC

Y90 Survival & PVT
gY90 – Long-term outcomes

Radioembolization with Yttrium-90 Glass Microspheres in Hepatocellular Carcinoma: European Experience on Safety and Long-Term Survival

• Hilgard 2010: gY90
  • Single center consecutive, observational longitudinal cohort Study
  • 108 patients; Intermediate and advanced age including PVT
  • CP –B7 mean overall survival approximately 6 months
    • (5.6 months in CP– B in Salem trials below)
  • Mean OS 16.4 m and TTP 10 months
  • TTP and survival comparable to the SHARP trial
  • Suggests combination with sorafenib therapy warranted.
Salem 2010 gY90 Longitudinal OS

- Single center, prospective, longitudinal cohort study.
- 291 patients
- CP-A (22mo), branch PVT (16.6mo), Main PVT (7.7mo), CP-B 5.6 months
- CP– A with or without PVT benefited the most.
- CP– B with PVT had poor outcomes.
Radioembolization for hepatocellular carcinoma with portal vein thrombosis: Impact of liver function on systemic treatment options at disease progression

- Memon 2012 gY90
  - Subset analysis of a 291 patient cohort (CP-A with PVT) of consecutive HCC patients treated with Y-90
  - Baseline PVT, ≤CP-B7, no extrahepatic metastases
  - 64% transitioned from CP-A to CP-B (liver function) at the time of imaging progression
    - Which would exclude them from CP-A required therapies/trials
  - The findings challenge the feasibility of sequentially treating patients with Y90 followed by systemic agents at progression.
    - If combining therapies consider adjuvant before progression of Dz.
    - Consider earlier **Staged Migration Strategy** {along BCLC}
Y90 & PVT → Survival data

- Mazzaferro 2013 gY90
  - Single center prospective phase 2 trial on consecutive cohort
  - 52 patients; Intermediate and advanced disease patients – BCLC B & C
  - 15 to 20% of potential candidates not fully treated because of arterial shunting (did not use intent-to-treat)
  - Median overall survival 15mo, 18 mo for intermediate stage and 13 mo for Advanced stage
  - BCLC - C patients with CP-A,
    - Segmental or Lobar PVT → mean OS 17 months.
    - Main portal vein → mean OS approximately 8 months.
Radioembolization as locoregional therapy for HCC

Data is for Glass Y90
- Y90 safe PVT & well tolerated
- OS CP-A, Segmental/Lobar PVT
  - OS~17mo
- Start systemic therapy prior to imaging progression in this treatment schema. (b/c of worsening liver function)

Take Home
Differences in IA-Locoregional therapy for HCC

Y90 vs cTACE
Y90 versus cTACE

Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma

• PREMIERE 2016 gY90 v cTACE:
  • Investor initiated, open label, single center, phase 2 prospective randomized study of chemoembolization versus radio embolization
  • 179 patient met enrollment criteria BCLC A/B without PVT
  • OS equivalent.
  • Y90 significantly longer TTP.
  • Y90 better QOL.

• Reminder:
  ➢ Intermediate stage patients are still a very heterogeneous population
Differences in IA-Locoregional therapy for HCC

- Y90 has better QOL scores
- Y90 significantly better TTP
  - (important for bridging to liver transplant)
Combined locoregional-medical therapy for HCC

TACE plus sorafenib

TACE Protocol
DEB/cTACE/TAE

Radioembolisation

Schedule
Before/after/simultaneous sequential/interrupted/continuous

TKIs & c-met
sorafenib/lenvatinib/regorafenib
cabozatinib

Immune modulator
Effector/inhibitor cells/cytokines

Blood biomarker

Modality
RFA/Cryo/TACE, HIFU/IRE

Tissue biomarker
prediction response
Combination TACE & sorafenib

• POST-TACE 2011:
  – Phase 3 trial prospective randomized controlled trial Analysis on an intent to treat
  – 458 patients; 229 patients per arm; Intermediate stage
    • CP – A and greater than 25% response to TACE
    • 1 - 3 months after TACE session (Approximately 9 weeks) randomized to placebo versus sorafenib → Delayed sorafenib dosing
  – Mean daily dose of sorafenib was 386 mg with 73% of patients having dose reductions and 91 having dose interruptions.
  – Mean drug administration was 17.1 wks for sorafenib and 20.1 wks for placebo
  – TTP was not significantly different sorafenib 5.4 and placebo 3.7 months.
  – Possible confounders; delayed starting drug and low daily dosage
Combination TACE & sorafenib

- **SPACE trial 2016**
  - International, multicenter, Phase 2 randomized, double-blind, placebo-controlled
  - 307 patients ~ 151 patient’s per arm
  - Intermittent stage (Unresectable, multinodular, asymptomatic HCC BCLC– B, CP– A)
  - Continuous – Sorafenib or placebo started day 1 and TACE administered on a fixed cycle. Bi-lobar HCC treated in a single session.
  - No significant difference in TTP
  - Subgroup analysis showed longer sorafenib treatment duration associated with improved TTP
Combination TACE & sorafenib

- **TACE-2 2017;**
  - Multicenter, randomized, placebo-controlled, phase 3 trial
  - *CP– A (aka the NEW BCLC Treatment guidelines)*
  - Randomized 121; Continuous oral sorafenib or matching placebo combined with TACE matched placebo
  - DEB-TACE performed 2 to 5 weeks post randomization
  - No significant differences in QOL scales.
  - No significant differences in progression free survival – approximately 235 days
Combined locoregional-medical therapy for HCC

TACE plus sorafenib

TACE Protocol
DEB/cTACE/TAE

Take Home

- 3 trials, each w/ weaknesses but none showed significant difference
- Combined treatment is safe
- Demand TACE on sorafenib is better
- Longer time on sorafenib with concomitant TACE is better
Differences in Radioembolization and Medical therapy for HCC

Y90 vs sorafenib
Combination rY90 versus sorafenib

**Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial**

- SARAH 2017;
  - Multicenter, open label, randomized phase 3 comparing Y90 with sorafenib in a two tailed Study designed for superiority/detriment with the primary endpoint overall survival
  - 467 patients - Western population.
  - Intermediate and advance disease patients
  - 30% in both arms at Main PVT.
  - The study failed to meet the primary endpoint (intent-to-treat ITT)
    - Media OS 8 mo (Y90) and 9.9 mo (sorafenib)
    - OS Y90 not superior, Better QOL in Y90
  - Relative treatment delay with Y90; approximately 25 days, time to sorafenib approximately 5 days → three-week difference in initiation of treatment (~10%)
• SIRveNIB 2017; OS Y90 not superior, AE’s shorter in Y90
  – Similar SARAH trial as above
  – 360 enrolled in the Asia Pacific region.
  – The study failed to meet the primary endpoint, in fact mean overall-
    survival in the
    • Intent-to-treat population was 8.8mo (rY90) in 10 mo (sorafenib)
    • Treated population 11.3mo (Y90) and 10.4 mo (sorafenib)
Differences in Radioembolization and Medical therapy for HCC

Take Home

• 2 trials with resin-Y90 → neither showed superiority or detriment
  • sorafenib favored intent-to-treat population
  • Y90 favored treated population
• Y90 did have better QOL
• Start sorafenib and Y90 in CP-A with segmental/lobar PVT only
Combined locoregional-medical therapy for HCC

Y90 plus sorafenib
Combination Y90 & sorafenib versus sorafenib

- SORAMIC trial phase III April 2018; negative (paper pending)
  - no clinical advantage to adding (SIRT) to standard sorafenib treatment compared with using sorafenib alone.
  - Subgroup showed a survival benefit for Y90+sorafenib
    - <65 years old, non-alcoholic etiology, no cirrhosis

Study Director Professor Jens Ricke, MD, at the International Liver Congress 2018 held April 11–15 in Paris, France.
Combination gY90 & sorafenib  versus sorafenib

- **STOP-HCC**
  - Glass ➔ **Results pending**
  - Interim analysis says ➔ keep going
Combined locoregional-medical therapy for HCC

Ablation/TACE plus Check-point inhibitor

Tissue biomarker
- prediction
- response

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Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma

• Duffy, Greten, Wood 2017
  • Tremelimumab CTLA-4 CPI (check-point-inhibitor)
  • Single center staged, safety and efficacy study to demonstrate whether Tremelimumab could be combined with ablation (thermal and intra-arterial).
    • First study combining immune checkpoint inhibitor with TACE.
  • Subtotal Ablation was unemployed in this advance stage setting, the hypothesis being that peripheral immune stimulation induced by the ablative procedure could be amplified by immune checkpoint blockade.
  • In lesions not subject to ablation or TACE, objective response was evaluated using RECIST criteria.
HCC does **not** generally contain tumor infiltrating Lymphocytes.

The effectiveness of Tremelimumab likely **depends** on the ability of activated immune cells to transit to the tumor interface.

In this study; **all** tumor biopsies in this study showed immune cell infiltration within the tumor – with a trend towards more after ablation.
Combination Ablation/TACE and Immunotherapy

This combined therapy was feasible and resulted in **objective tumor responses outside** of the ablated or embolized zone.
Combination Ablation/TACE and Immunotherapy

Encouraging clinical activity was seen with objective durable responses observed.

This combination therapy demonstrated intriguing clinical activity however relative contributions of ablation and Checkpoint inhibition therapy require further investigation.
## Open Locoregional and Immunotherapy Trials

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#### Combining nivolumab with TACE (DEB-TACE)
- In the USA, a phase I trial of this therapy enrolling.
  - nivolumab is administered intravenously every 2 weeks at a dose level of 240 mg. The trial is designed to evaluate the safety of this therapy in various schedules (NCT03143270).
  - HUP, MSKCC, Mayo, DanaFarber
## Open Locoregional and Immunotherapy Trials

Combining with gY90 and Nivolumab
- Northwestern University
- HCC CP-A or B B8 max

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**Combining with ablation and Nivolumab**

- Across the USA,
  - A Phase 3, Randomized, Double-blind Study of Adjuvant Nivolumab Versus Placebo for Participants With Hepatocellular Carcinoma Who Are at High Risk of Recurrence After Curative Hepatic Resection or Ablation
  - Recruiting 530 patients
Open Locoregional and Immunotherapy Trials

**Combining with ablation and Nivolumab**

- National Institutes of Health Clinical Center
  - A Pilot Study of Combined Immune Checkpoint Inhibition in Combination With Ablative Therapies in Subjects With Hepatocellular Carcinoma (HCC) or Biliary Tract Carcinomas (BTC)
  - 90 patients

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### Open Locoregional and Immunotherapy Trials

#### rY90 and Pembro
- Indiana, Chapel Hill and Seattle
  - A Pilot Study of Pembrolizumab in Combination With Y90 Radioembolization in Subjects With Poor Prognosis Hepatocellular Carcinoma With Preserved Liver Function.
  - 30 patients

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**TATE and anti-PD-1**
- University of California, Irvine → Nadine Abi-Jaoudeh, MD
  - Phase IIA Single-Arm Study of Treatment of Patients With Advanced Liver Cancer With a Combination of TATE (Transarterial Tirapazamine Embolization) Followed by an Anti-PD-1 Monoclonal Antibody
  - 80 patients
SR 4233 (tirapazamine/TATE) and cTACE

- Phase I dose escalating study of hypoxia-activating agent tirapazamine in combination with trans-arterial embolization in patients with intermediate stage hepatocellular carcinoma
  - N. Abi-Jaoudeh
- tirapazamine is the lead compound in a new class of bioreductive anticancer drugs
- The preferential tumor cell killing of tirapazamine is a result of its high specific toxicity to cells at low oxygen tensions.
  - Such hypoxic cells are a common feature of solid tumors, but not normal tissues, and are resistant to cancer therapies including radiation and some anticancer drugs.
- Combination of tirapazamine and embolization appears safe with a robust efficacy of 67% CR.
“Unraveling this complex threaded knot will require true team science, interdisciplinary partnerships and coeducation. Only a combined effort between experts in tumor immunology, hepatology and interventional oncology will enable defining more optimal therapies for patients with HCC - who until very recently had few effective options. Indeed, an exciting time to have coffee with an expert in another discipline.”

Please remember Surveillance

- Interval should be dictated by rate of tumor growth and tumor incidence in target population
- Surveillance recommended in specific target populations
- 6-month interval = reasonable and cost-effective