Aspirin improves liver function and survival after TAE of HCC

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Disclosures

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Off-label use of medications will be discussed.
Adjuvants for locoregional therapy

**Problems with current therapy:**
- High rate of recurrence after TACE / TAE.
- On average, only 65% of the tumor is necrotic after TACE of HCC smaller than 5 cm.
- Only 43% of individual lesions showed complete necrosis on histology.

Adjuvants for locoregional therapy

Escape mechanisms that allow tumor cells to survive TACE / TAE:

- Immune tolerance to necrotic tumor
- Ischemia-induced angiogenesis
- Increased anaerobic respiration

Possible solution:
Several FDA-approved medications block these escape mechanisms.
Goal: Find new adjuvant medications

- Determine if outpatient medications taken at the time of liver tumor embolization or ablation affect survival.

- Examine prescription and non-prescription medications, taken for reasons unrelated to the primary cancer diagnosis.
Treatment groups

Liver tumor TAE, radioembolization, and ablation (n=1092 patients)

- HCC initially treated with TAE (n=304 patients)
- Colorectal liver metastases initially treated with ablation (n=172 patients)
- NET liver metastases initially treated with TAE (n=199 patients)

- Colorectal liver metastases initially treated with radioembolization (n=67 patients)
- Other (not analyzed) (n=350 patients)
543 different medications taken at time of locoregional therapy
Medications that might improve locoregional therapy

543 medications taken by patients at time of locoregional therapy

- literature search for medications with effect on cancer pathways, ischemia, glucose metabolism, blood flow, angiogenesis, immune response, radiation damage, or heat damage

29 medications and medication classes
Examples of medication classes

**Immunomodulatory**
- aspirin (116 patients)
- other NSAIDs (106 patients)
- corticosteroids (68 patients)
- other immunosuppressants (20)
- G-CSF (21 patients)
- antiviral for hepatitis B or C (26)

**Glucose metabolism**
- insulin (59 patients)
- metformin (52 patients)
- other oral anti-diabetic agents (55)

**Blood flow**
- beta blocker (156 patients)
- calcium channel blocker (108)
- ACE inhibitor / ARB (144 patients)
- diuretic (138 patients)

**Radioprotective**
- anticoagulant (80 patients)
- NSAID
- corticosteroid (68 patients)
- ursodiol (43 patients)
- vitamin C (33 patients)
**Methods**

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>HCC TAE</th>
<th>Colorectal ablation</th>
<th>Colorectal Y90</th>
<th>NET TAE</th>
</tr>
</thead>
</table>

For patients taking versus not taking each medication, calculate:

- Kaplan Meier curves
- Patient characteristics: AJCC stage, Child Pugh score, comorbidities, ECOG status

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**29 medications and medication classes**

- statin
- beta-blocker
- CCB
- ACE inhibitor / ARB
- diuretic
- anticoagulant
- anti-platelet
- aspirin
- NSAID (excluding aspirin)
- corticosteroids
- non-corticosteroid immunosuppressants
- G-CSF
- antiviral (anti-hepatitis B/C)
- antiviral (not anti-hepatitis B/C)
- any antiviral
- any antibiotic
- metformin
- non-metformin oral antidiabetic agents
- insulin
- PPI
- gabapentin
- ursodiol
- levodopa/meso
- iron
- omega-3 polyunsaturated fatty acids
- folic acid
- cyanocobalamin
- vitamin C
- vitamin D

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Results: Medications that improve survival after locoregional therapy

| HCC TAE                     | Colorectal ablation | Colorectal Y90 | NET TAE | PPI 
|-----------------------------|---------------------|----------------|---------|------
| Beta blocker                | Beta blocker        | (none)         | (none)  |      
| Aspirin                     | (none)              | (none)         | (none)  |      
| Other NSAIDs                | (none)              | (none)         | (none)  |      
| Antiviral (hep B/C)         | (none)              | (none)         | (none)  |      

Bold medications remain statistically significant after Bonferroni correction for multiple comparisons \( p < 0.0017 \).
Results: Survival after TAE of HCC

$n = 304$ patients

$p = 0.0008$

Number at risk

<table>
<thead>
<tr>
<th>TAE:</th>
<th>262</th>
<th>168</th>
<th>108</th>
<th>56</th>
<th>29</th>
<th>10</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAE + aspirin:</td>
<td>42</td>
<td>23</td>
<td>19</td>
<td>10</td>
<td>7</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>
Results: Confounding variables

For patients taking versus not taking aspirin or beta blockers at the time of TAE, there was no difference in:

- AJCC stage
- Child Pugh score
- underlying liver disease
- ECOG performance status
- Charlson comorbidity index
- prior sorafenib
- prior liver resection
- selectivity of the embolization
Aspirin and cancer

• Chronic inflammation plays a key role in cancer development, and this can be blocked by NSAIDS (Weinberg 2014).

• Large randomized trials have shown that aspirin reduces death from colorectal cancer, pancreatic cancer, and other adenocarcinomas (Rothwell 2011).

References:
Aspirin mechanisms

- **Anti-inflammatory**: Aspirin reduces death from chronic liver disease, and reduces development of new HCC.

- **Anti-angiogenic**: Aspirin inhibits hypoxia-induced angiogenesis.

- **Anti-glycolytic**: Aspirin inhibits phosphofructokinase, decreases glucose consumption by tumor cells, and decreases viability of tumor cells.
## Aspirin mechanisms

HCC patients treated with TAE:

<table>
<thead>
<tr>
<th></th>
<th>Aspirin ($n=42$)</th>
<th>No aspirin ($n=262$)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial response (CR or PR)</td>
<td>88%</td>
<td>90%</td>
<td>0.6</td>
</tr>
<tr>
<td>Median time to progression</td>
<td>6.2 mo</td>
<td>5.2 mo</td>
<td>0.4</td>
</tr>
<tr>
<td>Initial site of progression</td>
<td>53% / 40% / 8%</td>
<td>48% / 42% / 11%</td>
<td>0.8</td>
</tr>
<tr>
<td>(treated lesion / other liver</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lesion / extrahepatic lesion)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression at time of death</td>
<td>88%</td>
<td>89%</td>
<td>1</td>
</tr>
</tbody>
</table>
Aspirin and liver function

n.s. $p > 0.05$

* $p \leq 0.05$

** $p \leq 0.01$

*** $p \leq 0.001$

Days after initial embolization

Total bilirubin

no aspirin

aspirin
Aspirin and liver function

• Retrospective and animal studies show decreased liver fibrosis in patients / animals taking aspirin.

References
Conclusion

• Aspirin and other NSAIDs were associated with improved survival when taken at the time of embolization for HCC.

• Aspirin was not associated with survival differences after locoregional therapy for NET or colorectal liver metastases.

• Aspirin might be hepatoprotective.
Clinical bottom line

• Consider starting HCC patients on aspirin 81 mg daily before TAE or TACE. (Use caution if history of bleeding or peptic ulcers)

• Baby aspirin does not need to be held before arterial access.

• Beta blockers should be used as first line therapy for peri-procedural hypertension.
Acknowledgements

Citations:
