Examination of Topoisomerase I (TOPO1) Expression in Metastatic GI Cancers

Abstract

Abstract # 643

Background: Irinotecan failed in Stage III colon cancer, but succeeds in Stage IV, to prolong survival. We propose that TOPO1 over-expression is a phenomenon of metastatic disease, and perhaps part of the epithelial-mesenchymal-transition (EMT) associated with metastatic phenotypes.

Method: 5029 colorectal (CRC), 3016 pancreatic, 848 gastric and 309 small bowel adenocarcinoma (SBA) patients were included in the study and tested centrally at a CLIA laboratory (Caris Life Sciences, Phoenix, AZ). A threshold of 2+ and 3+ (intensity and percent staining) and TOPO1 (116E) clone was utilized. TOPO1 was examined in primary and metastatic specimens. Two-tailed Fisher’s exact test was performed to test where proportions of positive results were different by subgroup (p≤0.05).

Results:

Table 1: Distribution of gender, age and proportion of primary versus metastatic specimens utilized for profiling and included in this analysis.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Frequency</th>
<th>Metastatic %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>30-50</td>
<td>500/1000</td>
<td>40%</td>
</tr>
<tr>
<td>Female</td>
<td>30-50</td>
<td>300/700</td>
<td>40%</td>
</tr>
</tbody>
</table>

Results, contd.

Figure 2. Biomarker Profiles of TOPO1 positive and negative CRC (A) and Pancreatic (B) cancers

Figure 3. Distribution of Intensity and % Staining of TOPO1 expression by IHC

Table 5: Distribution of gender, age and proportion of primary versus metastatic specimens utilized for profiling and included in this analysis.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Frequency</th>
<th>Metastatic %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>30-50</td>
<td>500/1000</td>
<td>40%</td>
</tr>
<tr>
<td>Female</td>
<td>30-50</td>
<td>300/700</td>
<td>40%</td>
</tr>
</tbody>
</table>

Results, contd.

Figure 4a-b. Representative Images of IHC and IHC staining for TOPO1 (A-B) colorectal cancer metastatic to the liver, (C-D) pancreatic cancer metastatic to the liver (E-F) gastric cancer metastatic to the liver (G-H) duodenal cancer metastatic to the lung (I-J)

Conclusions

- Upregulation and over-expression of TOPO1 increases with disease stage in colorectal and pancreatic cancers.
- The increased expression of TOPO1 explains the utility of topoisomerase agents in advanced disease and may account for the failure of this approach in the adjuvant paradigm.
- TOPO1 assessment may help identify which patients are more likely or less likely to benefit from an irinotecan-based approach. Not all patients express the marker in the metastatic setting, and some patients in the adjuvant setting might be selectable for irinotecan-based therapy using this approach.
- At the same time, the ability to identify TOPO1 over-expression in the advanced disease setting points to the utility of identifying which patients have cancers that are prime candidates for aggressive combination therapy with FOLFIRI and which patients are less likely to benefit from this approach.
- A “precision chemotherapy” approach to patients with advanced disease could be expanded to include TOPO1, and this analysis supports prospective evaluation of TOPO1 as a predictive marker using tissue obtained from metastatic sites.
- Physicians using this marker for treatment selection should be suspicious of negative TOPO1 results obtained from the primary tumor as opposed to a metastatic site.

References