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

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Abstract

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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 ≥30% (intensity and percent staining) and TOPO1 (1D6) 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:

		Primary	Metastatic
CRC	Positive	796/2230	1524/2799
	Frequency	36%	54%
		p=0.0001	
Pancreatic	Positive	457/1338	1070/1678
	Frequency	34%	64%
		p=0.0001	
Gastric Cancer	Positive	291/506	210/342
	Frequency	58%	61%
		p=0.2856	
SBA	Positive	59/140	79/169
	Frequency	42%	47%
		p=0.4239	

Conclusion: The EMT associated with the transition from primary to invasive metastatic disease appears to include upregulation of TOPO1, in some GI cancers, including CRC, pancreatic and gastric cancer. The paradoxical failure of adjuvant irinotecan in Stage III, the epithelial phase of the cancer, may be due to a smaller fraction of patient's whose cancers express this biomarker of response in that setting. A re-examination of irinotecan makes sense for a portion of stage III patients whose cancer expresses high levels of TOPO1 in the primary lesion. The recent superiority with regard to response rate and survival or FOLFOXIRI over FOLFOX alone in the stage IV setting raises renewed interest in whether patients with non-metastatic disease could derive a superior cure rate if suitably selected for FOLFOXIRI with a biomarker approach. At the same time, a large number of patients fail to express TOPO1 in the metastatic setting and perhaps should be spared irinotecan-based approaches including the use of FOLFOXIRI.

Background

- Topoisomerase I (TOPO1) is a nuclear enzyme which cleaves and re-ligates single strands of DNA.
- TOPOO1 is essential for replication and transcription during cell reproduction and DNA repair.
- Camptothecin derivatives, including irinotecan and topotecan, bind to TOPO1, preventing its function, thus leading to activation of apoptotic pathways.
- Irinotecan is a widely-used chemotherapy used in combination with other agents to treat many cancer types, including colorectal, pancreatic and others.

Methods

Profiling results for 3931 colorectal, 1643 pancreatic, 472 gastric and 241 small bowel (all adenocarcinomas) cancer patients were included in this retrospective analysis. Full analysis focused on patients with profiling results which included next-generation sequencing data, therefore total n varies slightly from original abstract. Testing was completed centrally at a CLIA laboratory (Caris Life Sciences, Phoenix, AZ). The cohort was sub-grouped based on TOPO1 IHC status (positive or negative), for which a threshold of ≥2+ and ≥30% (intensity and percent staining) and TOPO1 (1D6) clone was utilized. Data was also sub-grouped based on disease status (primary vs. metastatic specimens utilized for profiling). Pearson's chi-squared test (IBM SPSS Statistics, Version 23.0, Armonk, NY) was utilized to test for significant differences between subgroups (p≤0.05).

Results

Table 1. Clinicopathologic Characteristics of Patient Cohort Studied

		Primary			Metastatic		
	Total n (%)	n (%)	gender	Median Age [range]	n (%)	gender	Median Age [range]
All	6287	3010 (48)	M (53%); F (47%)	56 [24-90]	3277 (52)	M(52%); F(48%)	60[30-90]
Colorectal	3931	1915 (49)	M (53%); F (47%)	60[20-90]	2016 (51)	M (50%); F (50%)	59 [19-90]
Pancreatic	1643	668 (41)	M (53%); F (47%)	64 [28-90]	975 (59)	M (55%); F (45%)	63 [21-90]
Gastric	472	289 (61)	M (56%); F (44%)	62[20-90]	183 (39)	M (52%); F (48%)	60 [24-86]
SBA	241	138 (57)	M (59%); F (41%)	62[31-88]	103 (43)	M (56%); F (44%)	63 [29-87]

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

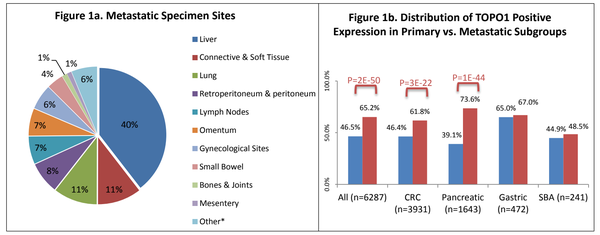
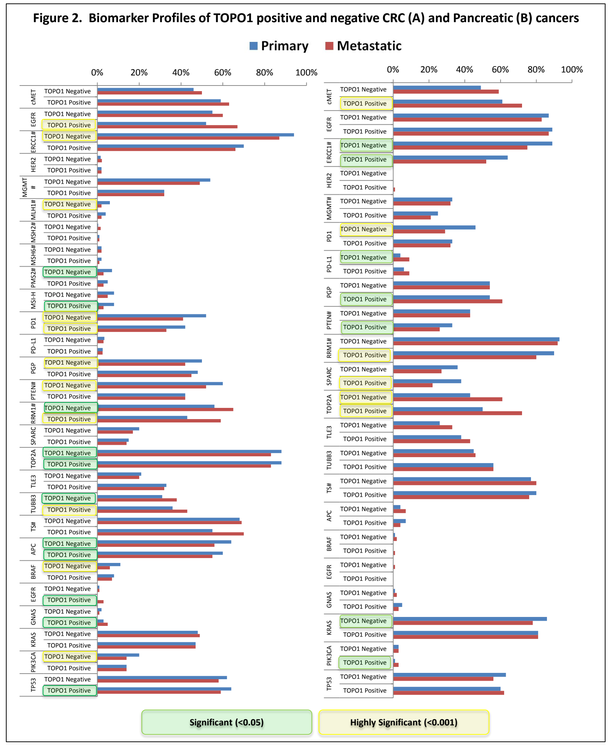
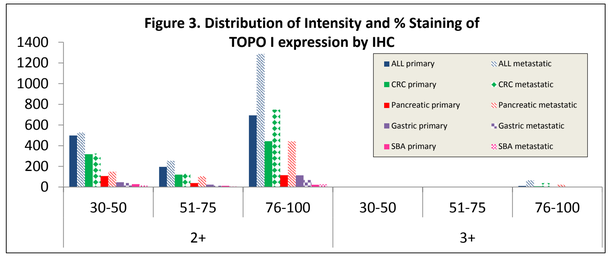


Figure 1a-b– Distribution of metastatic sites for specimens utilized for profiling (n=3277) and distribution of positive expression of TOPO1 in primary and metastatic samples (1b).

Results, contd.





Results, contd.

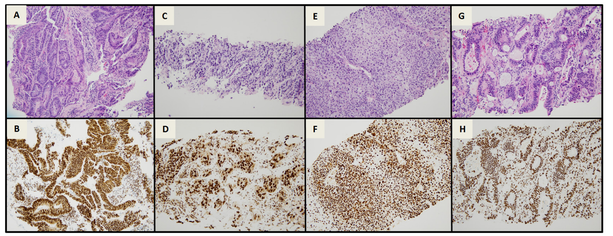


Figure 4A-H. Representative Images of H&E and IHC staining for TOPO1. (A-B) colorectal cancer metastatic to the lung, 3+ 90%; (C-D) pancreatic cancer metastatic to the liver (3+ 90%); (E-F) gastric cancer metastatic to the liver (2+ 100%) and (G-H) duodenal cancer metastatic to the lung (2+ 100%).

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 camptothecin agents in advanced disease and may account for the failure of this approach in the adjuvant randomized trials.
- TOPO1 assessment may help stratify 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 FOLFOXIRI 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

1. Pommier, Y. (2006). "Topoisomerase I inhibitors: camptothecins and beyond." Nature Reviews Cancer 6:789-802.
2. Kostopoulos, I., G. Fountzilas, et al. (2009). "Topoisomerase I but not thymidylate synthase is associated with improved outcome in patients with resected colorectal cancer treated with irinotecan containing adjuvant chemotherapy." BMC Cancer, 9:1-19.