Tumor profiling of gastric and esophageal carcinoma reveal different treatment options

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Abstract

Background: NCCN guidelines state that chemotherapies for esophageal and gastric carcinomas may be used interchangeably. We interrogated biomarkers from a large cohort of gastroesophageal cancer patients to identify similar and different alterations with therapeutic implications for gastric and esophageal cancers.

Methods: 666 gastric adenocarcinoma (GA) and 640 esophageal (553 adenocarcinoma, or EA, and 87 others) cases were evaluated by a combination of sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH/FISH).

Results: In the complete cohort of 1306 patients, 30 of 45 (66%) genes tested had mutations, with the highest rates seen in TP53 (54%), APC (10%), SMAD4 (5.9%), KRAS (5.9%) and PIK3CA (5.1%). Elevated IHC of TOP2A was seen in 76% of cases, TOPO1 in 51% and SPARC in 25%; decreased IHC of ERCC1 was seen in 65%, RRM1 in 62%, TS in 61% and MGMT in 45%, indicating benefit from epirubicin, irinotecan, nab-paclitaxel, platinums, gemcitabine, 5FU/capecitabine and temozolomide, respectively. In the HER2-positive cases, additional alterations were seen including low TS (50%), ERCC1 (63%), RRM1 (55%) and high TOPO1 (53%), indicating potential benefit from combining trastuzumab with 5FU/capecitabine, cisplatin, gemcitabine and irinotecan, respectively. When comparing EA to GA, select biomarkers showed a differential pattern between cancer types (Table 1), suggesting potential variability in efficacy of available therapeutic agents.

Conclusions: A multiplatform biomarker analysis identified common actionable targets in gastric and esophageal cancer as well as significant biomarker differences in EA and GA. This indicates the potential clinical impact of molecular profiling and highlights the need for separation of the two cancer entities for therapeutics.

Background

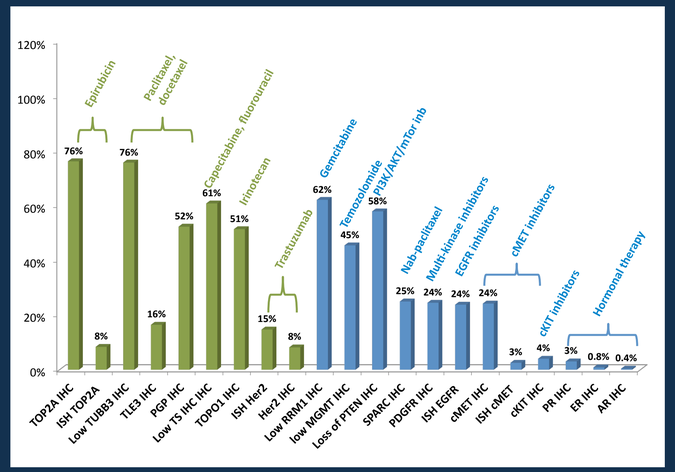
- Overall prognosis for gastro-oesophageal tumors remains poor
- Despite improved outcomes with multimodality therapies, tumor response rates to cytotoxic therapy continues to be sub-optimal (~40%)
- Aggressive nature of gastric (GC) and esophageal (EC) cancer makes selecting the optimal systemic chemotherapy regimen critical when attempting to prolong survival
- Systemic therapy regimens recommended by the NCCN are currently being used interchangeably for GC and EC.
- Emergence of molecular profiling has enabled clinicians to measure the activity of potential genetic targets in tumors for which systemic therapy agents are already available
- Study Objective: To compare the differential expression of chemotherapy associated biomarkers in GC and EC using a combination of sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH/FISH)

Methods

- GC and EC tissue samples were submitted to Caris Life Sciences (Phoenix, AZ) for tumor profiling analysis aimed to provide theranostic information. Retrospective biomarker analysis was performed on samples submitted from 2009-2013.
- Diagnoses were collected from referring physicians and classified at intake based on pathology and clinical history. Specific testing was performed per physician request and included a combination of sequencing (Sanger, NGS or pyrosequencing), protein expression (immunohistochemistry) and gene amplification (CISH or FISH).
- A total of 1306 samples were evaluated: 666 gastric adenocarcinoma (GA) and 640 esophageal carcinoma (553 adenocarcinoma (EA), 37 squamous carcinoma, 5 adenosquamous, 45 carcinoma NOS

Results

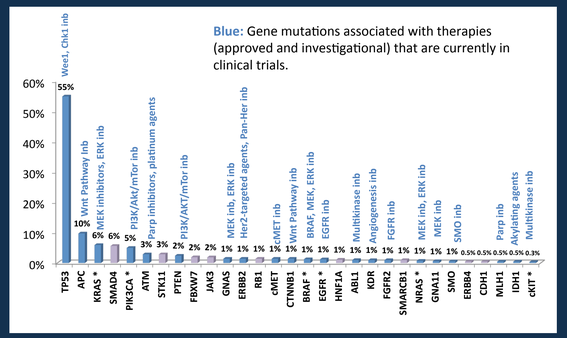
Figure 1: Overall actionable targets by IHC and FISH analysis and associated therapies (n=1306) : 17 IHC markers and 4 ISH markers were evaluated.



Green: agents that are on NCCN compendium for gastroesophageal cancers; Blue: Agents that are off NCCN compendium

Results

Figure 2: Gene mutations and associated clinical trials in gastro-oesophageal tumors(n=1306): 30 out of 45 genes sequenced showed mutations.



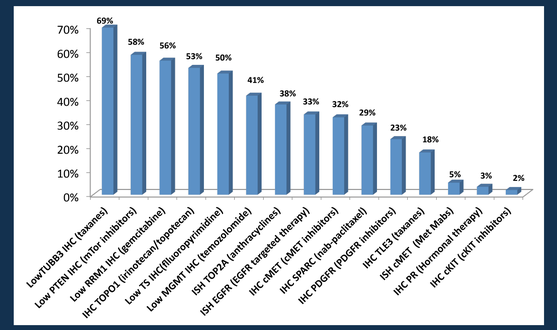
*: Combination of NextGen and Sanger Sequencing. **Gene tested without alterations:** AKT1, ALK, CSF1R, FGFR1, FLT3, GNAQ, HRAS, JAK2, MPL, NOTCH1, NPM1, PDGFRA, PTPN11, RET, VHL

Table 1: Biomarker comparison of gastric and esophageal adenocarcinoma: statistically significant biomarker differences are found when comparing EA to GA.

Target Biomarker	Associated Therapeutic Agent	EA (%*)	GA (%*)	p-value	Agents benefit GA or EA more?
IHC					
HER2	trastuzumab	13	4.6	<0.01	EA
SPARC	nab-paclitaxel	34	15	<0.01	EA
TOP2A	epirubicin	86	67	<0.01	EA
TOPO1	irinotecan	55	46	0.01	EA
MGMT	temozolomide	50	60	<0.01	EA
FISH					
HER2	trastuzumab	22	9	<0.01	EA
EGFR	cetuximab	33	16	<0.01	EA
SEQ					
KRAS	Cetuximab[&]	3.8	8.4	<0.01	EA
PIK3CA	mTOR inhibitors	2.4	7.8	0.04	GA
[&]lack of benefit					

EA: Esophageal adenocarcinoma, GA: Gastric adenocarcinoma, *: % Actionable

Figure 3: Actionable biomarker targets by IHC and FISH analysis among Her2+ gastro-oesophageal tumors: IHC and FISH tests identify combination therapy with trastuzumab in Her2+ cohorts



Conclusions

- **A multiplatform profiling of over 1,300 gastric and esophageal cancer patients identified effective treatments in both cancer types**
- **Interrogation of tumor biomarkers by IHC, FISH, and NGS analysis demonstrated significant differences in expression patterns between GC and EC, suggesting potential variation in tumor responsiveness to associated therapies**
- **Her2 and SPARC are significantly more prevalent in EA while PIK3CA mutation is more prevalent in GA, indicating differential responses to trastuzumab, nab-paclitaxel and PI3K/mTor inhibitors.**
- **Her2 positive Gastro-oesophageal cancers demonstrate a potential sensitivity to combination therapies of trastuzumab with platinum agents, irinotecan or fluoropyrimidine, highlighting IHC and ISH as possible diagnostic adjunct to further optimize systemic therapies**
- **Prospective controlled studies are needed to validate the role of these biomarkers in identifying effective cytotoxic agents for gastric and esophageal cancer**

REFERENCES

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