Gender differences in GI cancer

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One only sees what one looks for, one only looks for what one knows

J. w. v. Goethe

IN CONSEQUENCE: we ignore what we don’t know, and what we don’t look for
Structure

1. Introduction: WHY?
2. Sex differences in CANCER BIOLOGY
   a. Sexual dimorphism in cancer
   b. Gastric (G) /gastroesophageal (GEJ) cancer
   c. Colorectal cancer (CRC)
3. Sex differences in TREATMENT EFFECTS of GI cancer
4. Summary and conclusions
1. Introduction: WHY?

Mrs. C, 44 years

- Signet ring cell gastric carcinoma
- Total gastrectomy 11/2012
- pT4a pN3b (36/44) M1 R0, stage IV
- CAPOX 1-6/2013, poorly tolerated
- Meningeal carcinomatosis 06/2013
- Death in 07/2013
2. Sex differences in CANCER BIOLOGY
   a. SEXUAL DIMORPHISM IN CANCER

   - Significant sex differences in cancer susceptibility and survival, with men having an increased risk and poorer outcomes, exist in a wide range of cancer types

   - Sex-biased gene expression signatures in actionable genes have been detected in different types of cancers

2. Sex differences in BIOLOGY

b. gastric/GEJ cancers

Molecular subtypes are not equally distributed between men and women

Significantly higher rate of MSI among women confirmed in meta-analysis (n= 14.404; OR of MSI for women 1.57 (95% CI 1.31-1.89), p< 0.001)

2. Sex differences in BIOLOGY
b. gastric/GEJ cancers: CHROMOSOMAL INSTABLE (CIN)

- CIN esophageal, G and GEJ adenocarcinomas have similar chromosomal aberrations and lack dichotomizing features
- they account for a large part of all CIN tumors
2. Sex differences in BIOLOGY
b. gastric/GEJ cancers

ESOPHAGEAL ADENOCARCINOMA (EAC)

- Worldwide incidence 2012: 52,000 patients (41,000 men)
- STRIKING MALE PREDOMINANCE
- GERD as risk factor established in 1990s
- Associated with male adiposity
- But: male predominance persists even in lean individuals
- Hormones?

CONCLUSION: A mens’ distinct genetic, hormonal, anatomic … constitution, in combination with adiposity, predisposes to the development of E/ GEJ AC

Coleman et al., Gastroenterology 2018; Arnold et al., Gut, 2015; Xie et al., Clin Gastroenterol Hepatol 2016; Lagergren, 1999
2. Sex differences in BIOLOGY
b. gastric/GEJ cancers: GENOMICALLY STABLE/poorly cohesive

Retrospective analysis of 4722 pts. who underwent gastrectomy in Korea between 2005 and 2012
- Analysis of clinicopathological characteristics. TNM stage and type of surgery were balanced

Clinicopathological characteristics with significant sex disparity

<table>
<thead>
<tr>
<th>n = 4722</th>
<th>WOMEN (34%)</th>
<th>MEN (66%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean) (≤ 45)</td>
<td>55</td>
<td>57.9</td>
<td>&lt; .001</td>
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<tr>
<td></td>
<td>24</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>WHO: Well differentiated</td>
<td>30</td>
<td>50</td>
<td>&lt;.001</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Poorly differentiated</td>
<td>42</td>
<td>34</td>
<td>&lt;.001</td>
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<tr>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Signet ring cell carcinoma</td>
<td>28</td>
<td>16</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Kim, Ann Surg Oncol 2016
2. Sex differences in BIOLOGY
b. gastric/GEJ cancers: GENOMICALLY STABLE/ poorly cohesive GC

- Young women with GC have a worse overall survival
- Poor differenciation/ signet cell histology has a different prognostic impact in women

Kim, Ann Surg Oncol 2016
2. Sex differences in BIOLOGY
b. gastric/GEJ cancers: GENOMICALLY STABLE/ DIFFUSE

- Somatic genomic alterations associated with the unique characteristics of sporadic diffuse gastric cancers from younger patients were analyzed by whole-exome and RNA sequencing.

The predominance of diffuse histology and female sex in early onset gastric cancer may be related to frequent somatic mutations in CDH1 and TGFBR1.

Cho, Gastroenterology 2017
2. Sex differences in BIOLOGY
b. gastric/GEJ cancers

Differences in GE cancers arising in women and men include:

- The relative distribution of TCGA molecular subtypes
- Epidemiology and prognosis of tumors within a given subtype

**within CIN subtype:**
lower esophageal AC/GEJ more common in men

**within GS subtype:**
diffuse GC more common in young women, associated with poor prognosis
2. Sex differences in BIOLOGY
c. CRC

- Consensus molecular subtypes not equally distributed

- Among 1045 pat., w had more often younger age (p.<0.001), peritoneal metastases (p= 0.009), BRAF mutant tumors (p=.033) locoregional node involvement (p= 0.04). Among all RAS wild type, W had worse OS (31.7 vs 39.5 m)

3. Sex differences in TREATMENT EFFECTS Pharmacokinetics of 5-FU

- Men have a 26% higher elimination of 5-FU
- BSA based dosing results in:
  - 60% of pts. being underdosed
  - 15% being overdosed
  - 25% in the therapeutic range

Beumer, JH Clin Pharmacol Ther 2018; Mueller, F Cancer Chemotherapy and Pharmacology 2013
3. Sex differences in TREATMENT EFFECTS
A retrospective Analysis of the PETACC-3 trial

<table>
<thead>
<tr>
<th>Drug target</th>
<th>Total number of patients (n = 2974)</th>
<th>Male (n = 1656)</th>
<th>Female (n = 1318)</th>
<th>P-value*</th>
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</thead>
<tbody>
<tr>
<td>Leucopenia</td>
<td>All grade</td>
<td>38.9%</td>
<td>49.6%</td>
<td>&lt;0.0001</td>
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<td></td>
<td>Grade 3-4</td>
<td>2.4%</td>
<td>4.0%</td>
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<td>Neutropenia</td>
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<td>62.1%</td>
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<td>Grade 3-4</td>
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<td>22.2%</td>
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<tr>
<td>Anemia</td>
<td>All grade</td>
<td>49.5%</td>
<td>80.1%</td>
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<td>Grade 3-4</td>
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<tr>
<td>Thrombocytopenia</td>
<td>All grade</td>
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<td>2.3%</td>
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<tr>
<td></td>
<td>Grade 3-4</td>
<td>0.2%</td>
<td>0.2%</td>
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</tr>
</tbody>
</table>

Drug targets, but also the optimal dose to hit a target with an acceptable level of toxic effects may be different between men and women.
Association of sex and adverse events (AEs) of adjuvant chemotherapy in early stage colon cancer (CC): a pooled analysis of 28,636 patients (pts) in the ACCENT database

Women had a significantly greater risk of hematological and non-hematological AE’s

Example: Non-hematological Grade III/IV toxicities
3. Sex differences in TREATMENT EFFECTS: Role of genetic and nongenetic factors for 5-FU treatment-related severe toxicity

(n=683 pts)
- Determination of DPD splice mutation DPYD*2a, TYMS and MTHFR genotypes
- Result: Strong interaction between DPYD genetics and sex
- Toxicity in women independent of DPYD genotype, more likely to be explained by non-genetic factors

![Bar charts showing distribution of sex and distribution of DPYD*2A genotype by toxicity level.](Schwab, J Clin Oncol 2008)
3. Sex differences in TREATMENT EFFECTS
Pharmacokinetically based 5-FU dosing – the solution?
Randomized phase II-trial: Conventional versus pharmacokinetically-based dosing in mCRC

- N= 208. Concentration measurements at hour 3 and 7 after infusion start
- Primary endpoint: ORR 18.3 versus 33.7% ($p=.004$), median OS 16 vs 22 months in favor of patients treated with pharmacokinetically based dosing
- More toxicity in the conventional arm

Overall survival

Gamelin, J Clin Oncol 2008
3. Sex differences in TREATMENT EFFECTS
Perioperative treatment of gastric cancer

A pooled analysis of 3265 patients in four clinical trials (OEO 02, OEO 05, MAGIC, STO03):

Only 81 (versus 87%) of women completed chemotherapy, but 19 vs 13%, $p = 0.018$ obtained a TRG 1-2

Are men underdosed?
3. Sex differences in TREATMENT EFFECTS
Palliative treatment in CRC: The XELAVIRI-trial

N= 421 patients with metastatic CRC, randomization to
INITIAL COMBINATION: FOLFIRI/CAPIRI/bev versus
SEQUENTIAL ESCALATION: 5-FU/CAPE/bev, IRI added upon progression

WOMEN

MEN

Heinrich, K ASCO 2019
3. Sex differences in TREATMENT EFFECTS
Palliative treatment in CRC: The XELAVIRI-trial

CONCLUSION:
- Observed inverse treatment not explained by differences in pharmacokinetics or baseline characteristics
- Confirmation in large trials and/or databases necessary
- Differences in tumor biology?
- Differential effects of bevacizumab according to sex?

Heinrich, K et al., ASCO 2019
4. Summary and conclusions I

« Precision oncology is more than exploring molecular markers and targeted therapies…. A patients’ sex is a cost-free and well-known modulator of treatment response and –toxicity, that should be better understood and capitalized upon rather than overlooked »
MEN AND WOMEN ARE MORE THAN SUBGROUPS: Especially in diseases with significant differences in epidemiology or outcomes, men and women with non sex-related cancers should be considered as DISTINCT GROUPS OF PATIENTS, for whom different treatment strategies merit consideration.

INTERVENTIONAL CLINICAL TRIALS demonstrating the benefit of sex-specific dose modifications or treatment strategies ARE NECESSARY before any recommendation for clinical practice.
Thank you!