Refining the Management of Advanced Gastric Cancer

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Case: Background

• 40-year-old man presents with upper abdominal pain and unexplained weight loss of 6 pounds over 2 months
• Medical history of chronic gastritis, no history of familial cancer
• Esophagogastroduodenoscopy results reveal 4 ulcerated masses (6 cm) arising in the gastric cardia and extending into the gastric body in the lesser curvature of the stomach
• Biopsy results show poorly Helicobacter pylori–negative, HER2-negative poorly differentiated intestinal-type adenocarcinoma
• Computed tomography (CT) results show an enhanced mass in the lesser curvature of the stomach, lymphadenopathy along the gastrohepatic ligament, and multiple liver metastases up to 3 cm in size
• Laboratory: Hgb 11g/dL, AST and ALT 1.5 x ULN, bilirubin and renal function tests normal; CEA and CA 72-4 4 x ULN
• ECOG PS 1

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; Hgb, hemoglobin; PS, performance status; ULN, upper limits of normal
What would you recommend for first-line therapy for this young patient with metastatic HER2-negative gastric cancer?

1. Three drug docetaxel-based chemotherapy regimen (eg, DCF, DCX, DOF, DOX)

2. Three drug anthracycline-based regimen (eg, ECF, ECX, EOF, EOX)

3. Two drug chemotherapy regimen (eg, FOLFOX, cisplatin/5FU, cisplatin/capecitabine)

4. Clinical trial of targeted agent
Gastric Cancer Overview

• Gastric cancer is the fourth most commonly diagnosed cancer and the second most common cause of cancer-related deaths worldwide\textsuperscript{1,2}

• Despite an overall decrease in gastric cancer, there is a growing incidence of gastroesophageal junction (GEJ) tumors\textsuperscript{2-4}

• Metastatic gastric cancer has a poor prognosis
  – 2-year survival rate of around 20%\textsuperscript{1,4-5}
  – Median survival: <1 year\textsuperscript{6}
  – Overall survival (OS) improvement, 1975-77, 1984-86, 1999-2006
    \begin{align*}
    16\% \ & \rightarrow \ 18\% \ & \rightarrow \ 27\%
    \end{align*}

Metastatic Gastric Cancer

- 30% to 40% of patients present with stage IV disease due to the absence of effective screening
- No role for surgery given metastatic disease, unless primary tumor is bleeding or obstructing
- Systemic chemotherapy is the mainstay of therapy
- Median OS 10 months
Chemotherapy Regimens for Metastatic Disease

- CIV 5FU + cisplatin\textsuperscript{1-4}
  - 4-5 day to 6-week 5FU infusion
  - Response rate (RR) 20% to 40%
  - Median survival 7-10 months

- Adding a third drug
  - Epirubicin (ECF)\textsuperscript{5,6}: RR 40% to 45%, median survival 9 months
  - Docetaxel (DCF)\textsuperscript{7,8}: RR 37%, median survival 9 months
  - \textasciitilde 10% increment in RR
  - \textasciitilde 1-month increment in survival

- Capecitabine = 5FU, oxaliplatin = cisplatin

CIV, continuous intravenous infusion
Patient Outcome After First-Line Chemotherapy

Patient Selection for Chemotherapy

• Assess age, functional status, comorbidities
• Combination chemotherapy preferred over single agents
  — Monotherapy with 5FU, capecitabine, taxanes in elderly patients, patients with poor PS
• Three-drug regimens
  — High functional status, younger patients without comorbidities
  — Willingness to tolerate side effects
  — Access to frequent follow up and toxicity assessment
Case: Patient Treatment and Monitoring

- Patient initiated on epirubicin/oxaliplatin/capecitabine (EOX), which he tolerated relatively well
- Initial response included disease stabilization and clinical improvement
- Results from CT evaluation after 6th cycle of chemotherapy show progression of liver metastases
  - AST and ALT 2 x ULN, bilirubin normal, CEA and CA 72-4 6 x ULN
  - PS 1
Which of the following therapies would you recommend?

1. Single-agent chemotherapy
2. Reintroduction of an oxaliplatin-containing regimen (eg, FOLFOX)
3. Other combination chemotherapy (eg, FOLFIRI, docetaxel/cisplatin, docetaxel/irinotecan)
4. Paclitaxel + ramucirumab
5. Ramucirumab as a single agent
Second-Line Chemotherapy for Gastric Cancer

- **Cougar Trial-02 (UK)**
  - 168 patients with gastric and GEJ cancer
  - **BSC vs docetaxel** 75 mg/m² every 3 weeks
  - OS improved from 3.6 months → 5.2 months (HR 0.67, \( P = .01 \))
  - Responses in 7% of patients

- **Kang**
  - 202 patients with gastric cancer
  - **Docetaxel** 60 mg/m² every 3 weeks or **irinotecan** 150 mg/m² every 2 weeks vs **BSC**
  - OS improved from 3.8 months → 5.3 months (HR 0.657, \( P = .007 \))
  - RR 10% irinotecan, 17% for docetaxel

BSC, best supportive care; HR, hazard ratio; RR, response rate
Second-Line Chemotherapy: Paclitaxel vs Irinotecan

AGC refractory to prior FP confirmed by imaging
Age 20-75 years, PS 0-2, No history of irinotecan (CPT-11) or taxane

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Median</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly Paclitaxel (wPTX) 80 mg/m² d1, 8, 15 q4w</td>
<td>108</td>
<td>9.5 m</td>
<td>1.13 (0.86-1.49)</td>
<td>.38</td>
</tr>
<tr>
<td>Irinotecan (IRI) 150 mg/m² d1, 15 q4w</td>
<td>111</td>
<td>8.4 m</td>
<td></td>
<td></td>
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</tbody>
</table>

Log-rank test

AGC, advanced gastric cancer; FP, fluoropyrimidine plus platinum
Agents Targeting the VEGF Pathway

Anti-VEGF antibody (bevacizumab) → VEGF-A

Anti-VEGFR2 antibody (ramucirumab)

Soluble VEGF receptor (Ziv-aflibercept)

VEGFR-1, VEGFR-2, VEGFR-3

Endothelial cell

Small-molecule inhibitors of VEGFR
(regorafenib, PTK-787, cediranib, motesanib, sunitinib, sorafenib, pazopanib, axitinib, etc)

VEGFR, VEGF receptor
Bevacizumab for Gastric Cancer

- AVAGAST: Cape-Cisplatin + / - Bevacizumab
  - Negative trial failed to meet primary endpoint of improved OS
  - Improvements in RR and PFS
  - Trend toward improved OS in patients treated in the United States and South America

Next Generation VEGF Inhibitors

• Apatinib\(^1\)
  – Small-molecule multitargeted TKI with activity against VEGFR
  – 144 patients, placebo vs apatinib 850 mg/d or 425 mg BID
  – OS 2.5 months, 4.83 months, 4.27 months
  – RR 10%

• Ramucirumab, REGARD Trial\(^2\)
  – Humanized antibody blocking VEGFR2
  – 355 patients post 5FU or platinum-based chemotherapy
  – BSC vs ramucirumab 8 mg/kg IV every 2 weeks

TKI, tyrosine kinase inhibitor
REGARD Trial: Results

- Disease control rate improved from 23% to 49%
- Very low toxicity—8% grade ≥3 hypertension

RAINBOW: Phase III Study Design

**Important inclusion criteria:**
- Metastatic or locally advanced unresectable gastric or GEJ* adenocarcinoma
- Progression after first-line platinum/fluoropyrimidine-based chemotherapy

**Stratification factors:**
- Geographic region
- Measurable vs nonmeasurable disease
- Time to progression on first-line therapy (<6 months vs ≥6 months)

*Gastric and GEJ will be summarized under the term GC
RAINBOW: Overall Survival

**HR (95% CI) = 0.807 (0.678, 0.962)**
Stratified log rank *P*-value = .0169

<table>
<thead>
<tr>
<th></th>
<th>RAM + PAC</th>
<th>PBO + PAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients / events</td>
<td>330 / 256</td>
<td>335 / 260</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>9.63 (8.48, 10.81)</td>
<td>7.36 (6.31, 8.38)</td>
</tr>
<tr>
<td>6-month OS</td>
<td>72%</td>
<td>57%</td>
</tr>
<tr>
<td>12-month OS</td>
<td>40%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Δ mOS = 2.3 months

RAINBOW: PFS & Response Rates

HR (95% CI) = 0.635 (0.536, 0.752)
Stratified log rank P value < .0001

<table>
<thead>
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<th></th>
<th>RAM + PAC</th>
<th>PBO + PAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients / events</td>
<td>330 / 279</td>
<td>335 / 296</td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>4.40 (4.24, 5.32)</td>
<td>2.86 (2.79, 3.02)</td>
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<tr>
<td>6-Month PFS</td>
<td>36%</td>
<td>17%</td>
</tr>
<tr>
<td>9-Month PFS</td>
<td>22%</td>
<td>10%</td>
</tr>
<tr>
<td>Response rate</td>
<td>28%</td>
<td>16%</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>80%</td>
<td>64%</td>
</tr>
</tbody>
</table>

How Might Our Treatment Differ if This Patient Had Been HER2-Positive?

Expression of HER2 in Gastric Cancer

| Incidence of HER2 Expression by IHC or FISH \(^1-6\) |
|----------------------------------|------------------|
| All gastric cancer tumors        | —                |
| Histology                        |                  |
| Intestinal                       | 16% to 34%       |
| Diffuse                          | 6% to 7%         |
| Mixed                            | 20%              |
| Unknown                          | 14%              |
| Primary tumor location           |                  |
| GEJ                              | 25% to 34%       |
| Gastric                          | 9% to 20%        |

FISH, fluorescence in situ hybridization; IHC, immunohistochemistry
Results of the Phase III ToGA Trial

No. at risk

<table>
<thead>
<tr>
<th>Time, months</th>
<th>Event</th>
<th>FC + T</th>
<th>FC</th>
</tr>
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<tbody>
<tr>
<td>0-2</td>
<td>1.0</td>
<td>294</td>
<td>290</td>
</tr>
<tr>
<td>2-4</td>
<td>0.9</td>
<td>277</td>
<td>266</td>
</tr>
<tr>
<td>4-6</td>
<td>0.8</td>
<td>246</td>
<td>223</td>
</tr>
<tr>
<td>6-8</td>
<td>0.7</td>
<td>209</td>
<td>185</td>
</tr>
<tr>
<td>8-10</td>
<td>0.6</td>
<td>173</td>
<td>143</td>
</tr>
<tr>
<td>10-12</td>
<td>0.5</td>
<td>147</td>
<td>117</td>
</tr>
<tr>
<td>12-14</td>
<td>0.4</td>
<td>113</td>
<td>90</td>
</tr>
<tr>
<td>14-16</td>
<td>0.3</td>
<td>90</td>
<td>71</td>
</tr>
<tr>
<td>16-18</td>
<td>0.2</td>
<td>71</td>
<td>47</td>
</tr>
<tr>
<td>18-20</td>
<td>0.1</td>
<td>56</td>
<td>32</td>
</tr>
<tr>
<td>20-22</td>
<td>0.01</td>
<td>43</td>
<td>24</td>
</tr>
<tr>
<td>22-24</td>
<td>0.0</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>24-26</td>
<td>0.0</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>26-28</td>
<td>0.0</td>
<td>13</td>
<td>7</td>
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<td>28-30</td>
<td>0.0</td>
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<td>30-32</td>
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<td>6</td>
<td>5</td>
</tr>
<tr>
<td>32-34</td>
<td>0.0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>34-36</td>
<td>0.0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>36-</td>
<td>0.0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Event FC + T | 167 | 13.8 |
Event FC     | 182 | 11.1 |

Median Events | OS | HR   | 95% CI | P Value
---------------|----|------|--------|-------|
FC + T        | 167| 13.8 | 0.74   | 0.60, 0.91 | .0046 |
FC            | 182| 11.1 |

T, trastuzumab
Second-Line Treatment in HER2-Positive Gastric Cancer

• No standard therapy for second-line HER2+ gastric cancer previously treated with trastuzumab
  – Lapatinib (EGFR and HER2 inhibitor)
    • Demonstrated activity but did not statistically improve OS compared with paclitaxel\(^1\)
  – Pertuzumab (HER2 inhibitor): Clinical trials ongoing
  – Pertuzumab plus trastuzumab
    • Approved for metastatic breast cancer; phase II trial in gastric demonstrated activity\(^2\)
  – Trastuzumab emtansine (T-DM1): Clinical trials ongoing

Patient Case Continued: Response to Therapy

- Patient received paclitaxel + ramucirumab, which he tolerated well.
- Prior to the third cycle of therapy, the patient is diagnosed with grade 3 hypertension (blood pressure 180/100 mm Hg).
Patient Case Continued: Response to Therapy

- Patient received paclitaxel + ramucirumab, which he tolerated well
- Prior to the third cycle of therapy, the patient is diagnosed with grade 3 hypertension (blood pressure 180/100 mm Hg)

What would you do?

1. Continue paclitaxel + ramucirumab and give antihypertensive medication
2. Hold paclitaxel + ramucirumab until blood pressure is controlled
3. Continue paclitaxel, but hold ramucirumab until blood pressure is controlled
4. Continue treatment with ramucirumab in reduced dose
5. Discontinue ramucirumab permanently and continue paclitaxel alone
## RAINBOW: Adverse Events of Special Interest

<table>
<thead>
<tr>
<th>Category of Event †</th>
<th>RAM + PAC (n = 327)</th>
<th>PBO + PAC (n = 329)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade, %</td>
<td>Grade ≥3, %</td>
</tr>
<tr>
<td>Bleeding/hemorrhage</td>
<td>41.9</td>
<td>4.3</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>30.6</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25.1</td>
<td>14.7</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>16.8</td>
<td>1.2</td>
</tr>
<tr>
<td>GI hemorrhage</td>
<td>10.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Renal failure</td>
<td>6.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>5.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Venous thromboembolic</td>
<td>4.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Arteriothromboembolic</td>
<td>1.8</td>
<td>0.9</td>
</tr>
<tr>
<td>GI perforation</td>
<td>1.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>

† Each AESI category is composed of consolidated synonymous MeDRA preferred terms

Managing Adverse Events Associated With Angiogenesis Inhibitors

• Hypertension
  – Important to evaluate patients’ risk of developing hypertension prior to the start of therapy (eg, current medications, salt intake)
  – Preventive strategies best, including changes in diet and regular blood pressure monitoring
  – Use antihypertensives to manage hypertension, but avoid diuretics if possible
  – Dose reductions or treatment discontinuation should be used as needed if hypertension does not resolve

• Proteinuria
  – Evaluate baseline proteinuria
  – Test frequently (every 3 weeks to 4 weeks) using qualitative means such as dipstick test
    ▪ Use quantitative measure if levels increase
  – Discontinue therapy if grade 2+ proteinuria develops

Managing Adverse Events Associated With Angiogenesis Inhibitors (cont)

- Thrombotic events (TEs)
  - Prophylactic aspirin may be used for high-risk patients when there are no contraindications
  - With grade 3 or higher venous TEs, hold angiogenesis inhibitors while initiating anticoagulants, and resume when patient is stable
  - Therapy should be discontinued if any arterial TEs develop

- Bleeding, wound healing
  - Discontinue angiogenesis inhibition 6 weeks to 8 weeks prior to elective surgeries; wait 4 weeks after surgery to reinstate
  - Avoid anticoagulants when possible (in absence of TEs)
Though first-line treatment for gastric cancer has improved, patients will eventually relapse.

Targeted therapy represents an alternative to toxic chemotherapy combinations.

The anti-VEGFR antibody ramucirumab improves OS in patients who have progressed on first-line treatment.

Adverse events for ramucirumab are manageable with monitoring and dose reduction.

Several molecular pathways are being investigated for potential future therapies.