HAVE WE MADE ANY PROGRESS IN THE TREATMENT OF ADVANCED GASTRIC CANCER?

ESMO CONFERENCE: 11TH WORLD CONGRESS ON GASTROINTESTINAL CANCER
SESSION VII: GASTRIC CANCER
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HOSPITAL CLINICO
UNIVERSITY OF VALENCIA
SPAIN
BARCELONA, 25 JUNE 2009

Current Questions in Advanced Gastric Cancer Management

- Which are the aims of therapy?
- Should patients with advanced gastric cancer receive chemotherapy and when?
- Which are the main prognostic factors?
- Is primary tumor location relevant for treatment decisions?
- Which are the active drugs?
- Is there any standard combination of drugs?
- Why haven’t we been successful in getting better treatment for this disease?

Which are the aims of therapy?

- Symptomatic control
- Improve QoL or avoid its deterioration
- Delay tumor progression
- Prolong survival

Should patients with advanced gastric cancer receive chemotherapy?


When should patients with advanced gastric cancer receive chemotherapy?

<table>
<thead>
<tr>
<th>INITIAL ELF-FULV DELAYED CT AT PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
</tr>
<tr>
<td>TIME TO CT</td>
</tr>
<tr>
<td>QOL IMPROVEMENT</td>
</tr>
<tr>
<td>SURVIVAL</td>
</tr>
</tbody>
</table>


Is primary tumor location relevant for treatment decisions?


Figure 3. Overall survival according to primary tumour origin.
### What are the main prognostic factors?

<table>
<thead>
<tr>
<th>Group</th>
<th>Score</th>
<th>median OS</th>
<th>1-year Surv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>0</td>
<td>11.8 m</td>
<td>48.5%</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 o 2</td>
<td>7.4 m</td>
<td>25.7%</td>
</tr>
<tr>
<td>Poor</td>
<td>3 o 4</td>
<td>4.1 m</td>
<td>11.0%</td>
</tr>
</tbody>
</table>


Table 1. Multivariate Baseline Prognostic Model for REAL 2 Study Patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td>1</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>0:1</td>
<td>2.094</td>
<td>1.532 to 2.864</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>1.473</td>
<td>1.219 to 1.779</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peritoneal metastasis</td>
<td>1.918</td>
<td>1.210 to 3.041</td>
<td>0.001</td>
</tr>
<tr>
<td>Alkaline phosphatase &gt; 100 U/l</td>
<td>1.114</td>
<td>0.903 to 1.369</td>
<td>0.6</td>
</tr>
</tbody>
</table>


### Which are the active drugs?

- 5-Fluorouracil
- Oral Fluoropyrimidines (capecitabine, S1, UFT)
- Anthracyclines?
- Cisplatin
- Oxaliplatin
- Docetaxel
- CPT-11
- Transtuzumab
Monotherapy or combination of drugs?

What are the active drugs that have shown superiority in randomized trials?
- 5-Fluorouracil
- Oral Fluoropyrimidines (capecitabine, S1, UFT)
- Anthracyclines?
- Cisplatin
- Oxaliplatin
- Docetaxel
- CPT-11
- Transtuzumab

SPIRITS: Study Design

Central Randomization (dynamic balancing)
Adjustment Factors:
- Institute
- PS
- Unresectable vs Reseured

S-1 alone
S-1: 40-60 mg BID for 28 days q6wks

S-1 + CDDP
S-1: 40-60 mg BID for 21 days q5wks
CDDP: 60 mg/m² iv on day 8


Docetaxel-based chemotherapy in advanced gastric cancer: Phase III trial

Docetaxel-CF vs CF in advanced gastric cancer: Overall survival

Docetaxel-CF vs CF in advanced gastric cancer: Time to definitive Karnofsky PS deterioration


Docetaxel-CF vs CF in advanced gastric cancer: Time to 5% definitive Global Health status deterioration


ToGA trial design

HER2-positive advanced GC

5-FU or capecitabine + cisplatin (n=290)

Phase III, randomized, open-label, international, multicenter study

810 HER2-positive (22.1%) (n=584)

- Stratification factors
  - advanced vs metastatic
  - GC vs GEJ
  - measurable vs non-measurable
  - ECOG PS 0-1 vs 2
  - capecitabine vs 5-FU

Van Cutsem E, et al. ASCO 2009 abstract 4509

Primary end point: OS

Van Cutsem E, et al. ASCO 2009 abstract 4509

What are the active drugs that have shown non inferiority in randomized trials?

- 5-Fluorouracil
- Oral Fluropirimydines (Capcitabine, S1, UFT)
- Anthracyclines?
- Cisplatin
- Oxaliplatin
- Docetaxel
- CPT-11
- Transtuzumab

REAL-2: First line phase 3 trial in oesophagogastric cancer

Arm No. (ITT) Med, mo OS 1yr ORR, %

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF</td>
<td>263</td>
<td>9.9</td>
<td>37.7%</td>
<td>40.7%</td>
</tr>
<tr>
<td>EFO</td>
<td>250</td>
<td>9.3</td>
<td>40.4%</td>
<td>42.7%</td>
</tr>
<tr>
<td>ECX</td>
<td>245</td>
<td>9.9</td>
<td>40.8%</td>
<td>46.4%</td>
</tr>
<tr>
<td>EOX</td>
<td>244</td>
<td>11.2</td>
<td>48.6%</td>
<td>47.9%</td>
</tr>
</tbody>
</table>

Cunningham et al. NEJM 2008
**REAL-2: Overall survival fluoropyrimidin comparison**

HR for ITT population = 0.88 (0.77 – 1.00)

\[ p = 0.058 \]

*Cunningham et al, NEJM 2008*

**REAL-2: Overall survival platinum comparison**

HR for ITT population = 0.91 (0.79-1.04)

\[ p = 0.159 \]

*Cunningham et al, NEJM 2008*

**REAL-2: Overall survival: ECF vs EOX comparison**

HR: 0.80 (95% CI: 0.66-0.97)

Log rank \[ p = 0.02 \]

*Cunningham et al, NEJM 2008*

**5-FU CDDP VERSUS CAPECITABINE-CDDP. A RANDOMISED PHASE III NONINFERIORITY TRIAL (ML17032)**

Kang YK et al, Ann Oncol 2009

**5-FU VERSUS CAPECITABINE. A META-ANALYSIS OF REAL2 AND ML17032**

Okines AFC et al, Ann Oncol 2009

**5-FU, LV, Oxaliplatin (FLO) vs. 5-FU, LV, Cisplatin (FLP) in Advanced Gastroesophageal Adenocarcinoma**

Al-Batran SE et al, J Clin Oncol 2009
OXALIPLATIN VERSUS CISPLATIN
A RANDOMISED PHASE III TRIAL OF FLO VS FLP
PROGRESSION FREE SURVIVAL

Al-Batran SE et al, J Clin Oncol 2009

**OXALIPLATIN VERSUS CISPLATIN**
A RANDOMISED PHASE III TRIAL OF FLO VS FLP
OVERALL SURVIVAL

Al-Batran SE et al, J Clin Oncol 2009

HAVE WE MADE ANY PROGRESS IN THE TREATMENT OF ADVANCED GASTRIC CANCER?

**HAVE WE MADE ANY PROGRESS IN THE TREATMENT OF ADVANCED GASTRIC CANCER?**

- Transtuzumab + Chemotherapy
- 5-FU + LV + Oxaliplatin (FLO)
- Capecitabine + Cisplatin (XP)
- Docetaxel + Cisplatin + 5FU

**MEDIAN OVERALL SURVIVAL IN ADVANCED GASTRIC CANCER**

**ABSOLUTE INCREASE IN MEDIAN SURVIVAL IN ADVANCED GASTRIC CANCER**

**Recommended approach to advanced gastric cancer patients**
- Select patients with PS0-1 to participate in clinical trials
- CT should have a palliative role
- Patient reported outcomes of value
- Assess the risk of toxicity vs benefit
- TCF, ECF, EOX, XP or similar schedules of value
- Consider second line therapy for selected patients. More trials on this point are needed
Recommended approach to improve results on gastric cancer patients

- Design better clinical trials within academic and community centers
- International Cooperation
- Biological agents should be studied in randomized trials
- Further studies on better predictive and prognostic biomarkers

Thank you

Back up

5-FU VERSUS CAPECITABINE
A META-ANALYSIS OF REAL2 AND ML17032

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>5-FU</th>
<th>Capecitabine</th>
<th>Hazard ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td>0-1</td>
<td>2</td>
<td>1.38</td>
<td>1.87 (1.55-2.26)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;60 years</td>
<td>&gt;60 years</td>
<td>0.83 (0.73-0.94)</td>
<td>0.0286</td>
</tr>
<tr>
<td>Extent of disease</td>
<td>Locally advanced disease</td>
<td>Metastatic disease</td>
<td>1.64 (1.40-1.91)</td>
<td>0.0000</td>
</tr>
<tr>
<td>Tumor stage</td>
<td>T3N0</td>
<td>T2N1-M1</td>
<td>0.87 (0.77-0.98)</td>
<td>0.0229</td>
</tr>
<tr>
<td>Histopathological subtype</td>
<td>Adenocarcinoma</td>
<td>Squamous cell carcinoma</td>
<td>No significant effect</td>
<td></td>
</tr>
</tbody>
</table>

Okines AFC et al, Ann Oncol 2009

Docetaxel-CF vs CF in advanced gastric cancer: Progression free survival