NEO- AND ADJUVANT TREATMENT FOR GASTRIC CANCER: THE ROLE OF CHEMOTHERAPY

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ESMO Gastric Cancer Preceptorship Valencia 2019
DISCLOSURES

Honoraria
Astellas, BMS, Celgene, Five Prime Therapeutics, Servier, Gritstone Oncology
Lower oesophageal, gastroesophageal junction adenocarcinoma → ESMO Oesophageal Cancer Guidelines

Adenocarcinomas with epicenters no more than 2 cm into the gastric cardia are staged as oesophageal adenocarcinomas, and those extending further are staged as stomach cancers (AJCC 8th edition)

Gastric cancer → ESMO Gastric Cancer Guidelines
SURVIVAL FROM OG CANCER WITH SURGERY ALONE

Gastric cancer OS surgery alone

Oesophageal adeno OS surgery alone

Treatment in addition to surgery is required for most patients

ESMO GASTRIC CANCER GUIDELINES

Gastric Cancer

Operable stage T1N0

Consider endoscopic/limited resection

Operable stage >T1 N0

Preferred pathway

Preoperative chemotherapy

Surgery

Adjuvant chemotherapy

Adjuvant chemoradiotherapy

Postoperative chemotherapy

Surgery

Surgery

Inoperable or metastatic

Re-assess

Palliative chemotherapy

HER2-negative:
Platinum+ fluoropyrimidine-based doublet or triplet regimen

HER2-positive:
Trastuzumab + CF/CX

Second-line chemotherapy

Best supportive care if unfit for treatment

Consider clinical trials of novel agents

ESMO OESOPHAGEAL CANCER GUIDELINES

NEOADJUVANT AND PERIOPERATIVE CHEMOTHERAPY
AIMS OF NEOADJUVANT AND PERI-OPERATIVE CHEMOTHERAPY

- Downstage the tumour
- Increase R0 resection rate
- Treat micrometastatic disease
- Improve overall survival

Neoadjuvant and perioperative chemotherapy is more commonly used in non-Asian countries where tumours are frequently locally advanced and require downstaging prior to successful resection
EVOLUTION OF NEOADJUVANT AND PERI-OPERATIVE CHEMOTHERAPY 2002 - 2019

1. OE02 Trial Group, Lancet 2002

*chemotherapy patients; CF, cisplatin + 5-fluouracil; ECF epirubicin + CF; FLOT. 5-fluorouracil, leucovorin, oxaliplatin, docetaxel

2002
2 cycles neoadjuvant CF (OE02)

2006
3+3 cycles ECF (MAGIC)

2011
3+3 cycles CF (ACCORD)

2017
4+4 cycles FLOT (FLOT4)

5 year OS 23%*
5 year OS 36%*
5 year OS 38%*
5 year OS 45%*
PERI-OPERATIVE CHEMOTHERAPY VS. SURGERY ALONE
MAGIC AND FFCD/FNLCC

Eligible patients

3 cycles preoperative ECF (n=250)

Surgery alone (n=253)

Surgery

3 cycles postoperative ECF

3-6 week break

Eligibility criteria
Stage ≥ II gastric, GOJ, or lower oesophageal adeno (after 1999)
No metastases
ECOG 0-1

2-3 cycles preoperative CF (n=113)

Surgery alone (n=111)

Surgery

3 cycles postoperative CF

Eligibility criteria
Lower oesophageal or GOJ adeno (gastric after 1998)
No metastases
ECOG 0-1

ECF, epirubicin 50mg/m², cisplatin 60mg/m² and continuous 5-fluorouracil 200mg/m²/d
CF, cisplatin 100mg/m² and continuous 5-fluorouracil 800mg/m²/d day 1-5 q 28d

6-12 week break
PERI-OPERATIVE CHEMOTHERAPY VS. SURGERY ALONE EFFECT OF CHEMOTHERAPY ON POST-OPERATIVE STAGE

<table>
<thead>
<tr>
<th>MAGIC post-operative patient characteristics</th>
<th>FFCD/FNCLCC post-operative patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery alone</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>Curative</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>Palliative</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>Other</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>Surgery</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>Curative</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>Palliative</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>Other</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>ypT stage</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>T1</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>T2</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>T3</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>T4</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>ypN Stage (gastric)</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>N0</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>N1</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>N2</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>N3</td>
<td>Surgery alone</td>
</tr>
<tr>
<td>66/250 (66%)</td>
<td>11/193 (8%)</td>
</tr>
<tr>
<td>70/250 (28%)</td>
<td>55/193 (29%)</td>
</tr>
<tr>
<td>17/250 (6%)</td>
<td>16/193 (8%)</td>
</tr>
</tbody>
</table>

Peri-operative chemotherapy leads to tumour downstaging

ECF, epirubicin 50mg/m², cisplatin 60mg/m² and continuous 5-fluorouracil 200mg/m²/d
CF, cisplatin 100mg/m² and continuous 5-fluorouracil 800mg/m²/d day 1-5 q 28d
PERI-OPERATIVE CHEMOTHERAPY VS. SURGERY ALONE
EFFECT OF CHEMOTHERAPY ON OVERALL SURVIVAL

Overall survival
HR 0.75 (95% CI 0.60 - 0.93)
P=0.0001

Absolute gain in 5 year survival 13% (23% surgery alone to 36% chemotherapy plus surgery)

Absolute benefit in OS 14% (24% surgery vs. 38% chemo + surgery)

**AIO/FLOT4 TRIAL**

- Gastric cancer or adenocarcinoma of the gastro-esophageal junction type I-III
- Medically and technically operable
- cT2-4/cN-any/cM0 or cT-any/cN+/cM0

**FLOT x4 - RESECTION - FLOT x4**

- FLOT: docetaxel 50mg/m², d1; 5-FU 2600 mg/m², d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, every two weeks

**ECF/ECX x3 - RESECTION - ECF/ECX x3**

- ECF/ECX: Epirubicin 50 mg/m², d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m² p.o. divided into two doses d1-d21), every three weeks

Stratification: ECOG (0 or 1 vs. 2), location of primary (GEJ type I vs. type II/III vs. stomach), age (< 60 vs. 60-69 vs. ≥70 years) and nodal status (cN+ vs. cN-).

Primary endpoint OS (ITT)

**WHO ARE THE PATIENTS IN FLOT4?**

<table>
<thead>
<tr>
<th></th>
<th>ECF/ECX N=360</th>
<th>FLOT N=356</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age median</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=70</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>87</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>24%</td>
<td>24%</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>265</td>
<td>268</td>
</tr>
<tr>
<td></td>
<td>74%</td>
<td>75%</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>254</td>
<td>246</td>
</tr>
<tr>
<td></td>
<td>71%</td>
<td>69%</td>
</tr>
<tr>
<td>1</td>
<td>103</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td>29%</td>
<td>31%</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEJ Siewert type 1</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>24%</td>
<td>23%</td>
</tr>
<tr>
<td>GEJ Siewert type 2/3</td>
<td>115</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td>32%</td>
<td>33%</td>
</tr>
<tr>
<td>Stomach</td>
<td>160</td>
<td>158</td>
</tr>
<tr>
<td></td>
<td>44%</td>
<td>44%</td>
</tr>
</tbody>
</table>

Median age 62, younger than most gastroesophageal patients

But...24% were >70 years

99%+ were PS 0-1

50:50 split stomach vs junctional adeno
## FLOT IMPROVES SURGICAL OUTCOMES

<table>
<thead>
<tr>
<th></th>
<th>ECF/ECX (n=360)</th>
<th>FLOT (n=356)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection surgery</td>
<td>313/360 (87%)</td>
<td>336/356 (94%)</td>
<td>0.001</td>
</tr>
<tr>
<td>R0 resection rate</td>
<td>276/360 (77%)</td>
<td>300/356 (84%)</td>
<td>0.011</td>
</tr>
<tr>
<td>Any surgical complication</td>
<td>188/341 (55%)</td>
<td>188/345 (55%)</td>
<td></td>
</tr>
<tr>
<td>Death 90 days</td>
<td>26 (8%)</td>
<td>16 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

FLOT chemotherapy increases:
- % patients who undergo surgery
- % patients with R0 resection
- Surgical morbidity and mortality was not increased with FLOT

<table>
<thead>
<tr>
<th></th>
<th>ECF/ECX (n=360)</th>
<th>FLOT (n=356)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ypT stage ≤T1</td>
<td>53 (15%)</td>
<td>88 (25%)</td>
<td>0.001</td>
</tr>
<tr>
<td>ypN stage N0</td>
<td>146 (41%)</td>
<td>174 (49%)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

FLOT increases the % of patients have pathological early stage tumours compared to ECF/X

FLOT IMPROVES PFS AND OS COMPARED TO ECF/X

Projected PFS rates

<table>
<thead>
<tr>
<th></th>
<th>ECF/X</th>
<th>FLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 year</td>
<td>43%</td>
<td>53%</td>
</tr>
<tr>
<td>3 year</td>
<td>37%</td>
<td>46%</td>
</tr>
<tr>
<td>5 year</td>
<td>31%</td>
<td>41%</td>
</tr>
</tbody>
</table>

Projected OS rates

<table>
<thead>
<tr>
<th></th>
<th>ECF/X</th>
<th>FLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 year</td>
<td>59%</td>
<td>68%</td>
</tr>
<tr>
<td>3 year</td>
<td>48%</td>
<td>57%</td>
</tr>
<tr>
<td>5 year</td>
<td>36%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Progression free survival
18 months ECF/ECX vs 30 months FLOT
HR 0.75 (0.62-0.91) p=0.003

Overall survival
37 months ECF/ECX vs 50 months FLOT
HR 0.77 (0.63-0.94) p=0.012

# FLOT VS ECF/X TOXICITY

<table>
<thead>
<tr>
<th>Grade 3-4 &gt;5%</th>
<th>ECF/ECX (N=354)</th>
<th>FLOT (N=354)</th>
<th>P-value (Chi-Square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>13 (4%)</td>
<td>34 (10%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27 (8%)</td>
<td>7 (2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>55 (16%)</td>
<td>26 (7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Infections</td>
<td>30 (9%)</td>
<td>63 (18%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>139 (39%)</td>
<td>181 (51%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sensory</td>
<td>7 (2%)</td>
<td>24 (7%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>22 (6%)</td>
<td>9 (3%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anemia</td>
<td>20 (6%)</td>
<td>9 (3%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

FLOT increased diarrhoea, neutropenia and neuropathy
ECX increased nausea, anaemia and thromboembolic complications

PERIOPERATIVE CHEMOTHERAPY TOLERABILITY
CF, ECF/X AND FLOT

1. ~10% of patients will not complete pre-operative chemotherapy
2. Approximately 50% of patients are not fit enough for post operative chemotherapy

4. Petrillo et al, Cancers 2019
A NEW HORIZON FOR PERIOPERATIVE CHEMOTHERAPY IN ASIA

PRODIGY TRIAL

Neoadjuvant DOS + adjuvant S1 could be an option for locally advanced GC in Asia

Kang et al, ESMO 2019
ANOTHER NEW HORIZON FOR PERIOPERATIVE CHEMOTHERAPY IN ASIA

RESOLVE TRIAL

Perioperative SOX could be an option for locally advanced GC in Asia
SOX could replace XELOX for adjuvant treatment

Ji et al., ESMO 2019
PERI-OPERATIVE CHEMOTHERAPY: TAKE HOME MESSAGES

FLOT is the new gold standard treatment for patients who receive peri-operative chemotherapy and surgery for operable gastroesophageal cancer. In patients are not suitable for triplet chemotherapy, doublet chemotherapy can be considered. Doublets can be cisplatin or oxaliplatin based.

5 year projected OS with FLOT is 45%, therefore there is still more work to do to improve survival for patients treated with peri-operative chemotherapy.
ADJUVANT CHEMOTHERAPY
ESMO GASTRIC CANCER GUIDELINES

Gastric Cancer

Operable stage T1N0
Consider endoscopic/limited resection

Operable stage >T1 N0
Preferred pathway

Preoperative chemotherapy

Surgery

Adjuvant chemoradiotherapy

Adjuvant chemotherapy

Postoperative chemotherapy

Inoperable or metastatic

Re-assess

Palliative chemotherapy

Best supportive care if unfit for treatment

HER2-negative:
Platinum+
fluoropyrimidine-based
doublet or triplet regimen

HER2-positive:
Trastuzumab+
CF/CDX

Consider clinical trials of novel agents

Second-line chemotherapy
EVOLUTION OF NEOADJUVANT AND PERI-OPERATIVE
CHEMOTHERAPY 2002 - 2019

2001
Adjuvant 5FU + RT (INT 0116)

2005
12 months adjuvant S1 (ACTS-GC)

2012
6 months adjuvant XELOX (CLASSIC)

2018
6 months D-S1 then 6 months S1 (JACCRO-07)

ADJUVANT TRIALS IN GASTRIC CANCER

**ACTS-GC**
- Post-operative eligible patients
  - 1 year S1 (n=529)
  - No further treatment (n=530)

**Primary Endpoint**
Overall survival

**Secondary endpoints**
Relapse free survival & safety

**Eligibility criteria**
Stage ≥ II (no T1), IIIA or IIIB gastric adenocarcinoma
D2 resection minimum

**CLASSIC**
- Post-operative eligible patients
  - 6 months CapeOx (n=520)
  - No further treatment (n=515)

**Primary Endpoint**
3 year disease free survival

**Secondary endpoints**
Overall survival & safety

**Eligibility criteria**
Stage ≥ II, IIIA or IIIB gastric adenocarcinoma
D2 resection minimum

---

S1, 40mg/m²/d x 28 days followed by 2 week break x 1 year
CapeOx, capecitabine 1000 mg/m² bd  D1-14 , plus oxaliplatin 130 mg/m² iv D1 q3wks

IMPROVEMENTS IN SURVIVAL WITH ADJUVANT CHEMOTHERAPY

**ACTS-GC**

- **Update ESMO 2017 OPAS-1 study**
  - 6 months of S1 not inferior to 12 months

**CLASSIC**

- **Updated 5 year survival S1 vs surgery alone**
  - All patients 5 year OS 72% vs. 61%
  - Stage II 5 year OS 84% vs 71%
  - Stage IIIA 5 year OS 67% vs 57%
  - Stage IIIB 5 year OS 50% vs 44%

- **5 year updated survival CapeOx vs surgery alone**
  - All patients 5 year OS 78% vs 69%
  - Stage II 5 year OS 88% vs 79%
  - Stage IIIA 5 year OS 70% vs 63%
  - Stage IIIB 5 year OS 66% vs 45% (compare ACTS GC 50% vs. 44%)

S1 VS. S1-DOCE TAXEL ADJUVANT CHEMOTHERAPY  
JACCRO-7

Post-operative eligible patients

S1 80mg/m² d1-28 q 6 wks x 1 year  
(n=459)

Cycle 1: S1 80mg/m² d1-14 q21d

Cycle 2-7: docetaxel 40mg/m² plus S1 80mg/m² d1-14 q21d
Then S1 x 6 months  
(N=456)

Primary Endpoint
3 year relapse free survival

Secondary endpoints
Overall survival & safety

Relapse free survival

HR, 0.632; 99.99% CI, 0.400 to 0.998; P < .001)  
3-year RFS of 66% vs 50% in favour of docetaxel-S1

Overall survival not mature

Yoshida et al, JCO 37, no. 15 (May 20 2019) 1296-1304. Kodera et al, ASCO 2018
Neoadjuvant or peri-operative chemotherapy is preferred due to the downstaging effects associated with this.

The GASTRIC group meta-analysis suggests a 5.8% absolute OS benefit at 5 years (55.3% to 49.6%) for patients treated with adjuvant chemotherapy.

CHEMOTHERAPY VS. CHEMORADIOThERAPY
CHEMOTHERAPY VS CHEMORADIOOTHERAPY
An ongoing debate

For **GASTRIC** adenocarcinomas **peri-operative chemotherapy (FLOT)** is preferred to post-operative chemotherapy or post-operative chemoradiotherapy because:

- More patients are able to receive chemotherapy before surgery than afterwards.
- Downstaging due to chemotherapy increases rates of R0 resections

However, in cases where surgery has been performed without neoadjuvant chemotherapy, adjuvant treatment may be considered.

For **GASTROESOPHAGEAL JUNCTIONAL** (Siewert Type I/II) and **OESOPHAGEAL** adenocarcinoma

**Perioperative chemotherapy and neoadjuvant chemoradiotherapy are both reasonable choices**

Patients selection for treatment depends on the characteristics of the patient, the tumour and local expertise
The NeoRes study treated patients with oesophageal SCC and adenocarcinoma including gastroesophageal junction. Although underpowered for survival, no difference was suggested in OS for chemotherapy vs chemoradiotherapy treated patients, nor in subgroup analysis. Surgical complications were more severe, but not more frequent in patients treated with chemoradiotherapy.

CHEMOTHERAPY VS CHEMORADIOHERAPY

Propensity matched analysis neoadjuvant chemotherapy vs CRT

Eligible patients from prospectively maintained databases
OAC or Siewert I/II GEJ

Neoadjuvant chemotherapy plus surgery
N=221

Neoadjuvant chemoradiotherapy plus surgery
N=221

This multicentre European analysis matched patients with resectable oesophageal and Siewert Type I and II junctional cancers treated with neoadjuvant chemotherapy or chemoradiotherapy.

Compared with chemotherapy CRT is associated with improvements in R0 resection rates and pathological complete response, but not in overall survival.

With the exception of anastamotic leaks, morbidity and post-operative mortality were not different between the groups.

Trials which will answer this question
Chemo vs CRT

Neo-Aegis (NCT01726452): Same design (n=594)

Neoadjuvant Radio-CTX – CROSS Regimen
RESECTION

Primary endpoint: survival
3-year-OS-rate
55% CROSS vs. 68% FLOT

Perioperative CTX: FLOT* 4 x pre and post
RESECTION

N=438
T1N1M0
or
T2–4aN0–1M0

Trials which will answer this question
Peri-operative chemo vs peri-operative chemo +RT

TOPGEAR

Eligibility
Resectable stomach or gastroesophageal adenocarcinoma

Preoperative chemotherapy
Chemotherapy ECF/X (FLOT) 2 cycles
Chemotherapy ECX/X (FLOT) 3 cycles

Preoperative radiotherapy (1 arm only)
Chemoradiotherapy 45Gy + 5FU/X

Postoperative chemotherapy
Chemotherapy ECF/X (FLOT) 3 cycles
Chemotherapy ECX/F FLOT 3 cycles

FLOT to replace ECF/X

BIOMARKERS FOR PERIOPERATIVE CHEMOTHERAPY
BIOMARKERS FOR PERIOPERATIVE CHEMOTHERAPY

- ctDNA
- Signet ring
- MSI
- Lymph nodes
- TRG
- Gene profiles
NEOADJUVANT CHEMOTHERAPY FOR SIGNET CELL CANCERS

PRODIGE 19

- Study met primary endpoint
- No detriment to upfront chemotherapy

**Take home message**
No contraindication to periop chemotherapy in SRC

Eveno et al, ASCO 2019, Al Batran et al, Lancet 2019
RISK STRATIFICATION USING TUMOUR REGRESSION GRADING

Lymph nodes are the most important prognostic marker following chemotherapy and surgical resection.
MSI FOR PERSONALISED TREATMENT IN RESECTABLE GC

MAGIC Trial

CLASSIC Trial

No benefit to perioperative chemotherapy in MSI-H patients

No benefit to adjuvant chemotherapy in MSI-H gastric patients

Smyth et al, JAMA Oncol. 2017 Sep 1;3(9):1197-1203.
META-ANALYSIS OF MAGIC, CLASSIC, ITACA-S AND ARTIST OS IN MSI VS MSS PATIENTS

A

ALL TRIALS

B

MAGIC AND CLASSIC

PROGNOSTIC AND PREDICTIVE GENE SIGNATURES IN CLASSIC

Prognostic

Predictive

ctDNA detectable with targeted panel in 17/29 locally advanced patients with tumour naïve panel

After surgery 7/22 patients had detectable ctDNA, of these DFS was shorter than patients with no ctDNA detected

3 patients with ctDNA positivity did not recur –clonal haemoatopoesis (CHIP) likely

Larger series and personalised panels may be more sensitive and specific

BIOMARKERS

Take home messages

- Lymph node metastases are a more important prognostic marker than tumour regression grade

- Mismatch repair deficient tumours do not appear to benefit from perioperative or neoadjuvant chemotherapy

- Gene signatures and ctDNA show promise for selection for chemotherapy, however require prospective validation.