Oxaliplatin in Elderly colorectal cancer patients

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GERCOR - GEPOG
Acknowledgments:

- Pr Aimery de Gramont  
  CHU St Antoine – Paris
- Dr Thomas Aparicio  
  CHU Bichat – Paris
- Dr Tristan Cudennec  
  CHU Ambroise Paré – Paris
- Pr Hervé Curé  
  Institut Jean Godinot - Reims
- Dr Frédérique Maindrault  
  CHU St Antoine - Paris
- Dr François Morvan  
  CH Pontoise - Paris
- Dr Nathalie Perez  
  CHU St Antoine - Paris
- Dr Frédérique Rousseau  
  Centre Paoli Calmette - Marseille
- Pr Laurent Teillet  
  Hôpital Ste Perrine - Paris
- Dr Christophe Tournigand  
  CHU St Antoine - Paris
- Dr Florence Woerth  
  CH Senlis
Colorectal cancer (CRC): an Elderly Disease

CRC is the third most common cancer in the world with 800,000 new cases/year.

In France, 36,000 new cases/year of CRC:

- 60% after 70 years
- 43% after 75 years
- 11% after 85 years

## CRC in Elderly: Undertreated!

<table>
<thead>
<tr>
<th>Côte d’Or department (1997-1998) (1)</th>
<th>% of patients treated with chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 75 years</td>
</tr>
<tr>
<td>Stade II CCR</td>
<td>4,9%</td>
</tr>
<tr>
<td>Stade III CCR</td>
<td>24,4%</td>
</tr>
<tr>
<td>Metastatic disease 1988-89 (2)</td>
<td>8%</td>
</tr>
</tbody>
</table>


Oxaliplatin: First Line Agent in Advanced Colorectal Cancer

LV5FU2 vs FOLFOX 4: PFS

Is it True In Elderly Patient?
## FOLFOX4 in Elderly Patients with Colon Cancer: A Pooled Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparator regimen</th>
<th>Setting</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOSAIC&lt;sup&gt;1&lt;/sup&gt;</td>
<td>5-FU/LV</td>
<td>Adjuvant</td>
<td>2246</td>
</tr>
<tr>
<td>N9741&lt;sup&gt;2&lt;/sup&gt;</td>
<td>IFL</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Line</td>
<td>546</td>
</tr>
<tr>
<td>de Gramont&lt;sup&gt;3&lt;/sup&gt;</td>
<td>5-FU/LV</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Line</td>
<td>420</td>
</tr>
<tr>
<td>Rothenberg&lt;sup&gt;4&lt;/sup&gt;</td>
<td>5-FU/LV</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Line</td>
<td>530</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>3742</td>
</tr>
</tbody>
</table>

<sup>1</sup> André et al, NEJM 2004; <sup>2</sup> Goldberg et al, JCO 2004; <sup>3</sup> de Gramont et al, JCO 2000; <sup>4</sup> Rothenberg et al, JCO 2003
Progression or Disease Free Survival

Forest plot of progression or disease-free survival by study for oxaliplatin plus fluorouracil/leucovorin administered bimonthly vs control by age. de Gramont, de Gramont et al.; MOSAIC, Multicenter International Study of Oxaliplatin/SFU-LV in the Adjuvant Treatment of Colon Cancer; Rothenberg, Rothenberg et al.; Goldberg, Goldberg et al.

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Overall Survival

Forest plots of overall survival by study for oxaliplatin plus fluorouracil/leucovorin administered bimonthly versus control by age. de Gramont, de Gramont et al.; Rothenberg, Rothenberg et al.; Goldberg, Goldberg et al.
Adverse Events (Gr ≥ 3)

- Neutropenia: Age < 70 (p = 0.04), Age > 70 (p = 0.08)
- Thrombocytopenia: Age < 70 (p = 0.37), Age > 70 (p = 0.38)
- Fatigue: Age < 70 (p = 0.38), Age > 70 (p = 0.20)
- Neurotoxicity: Age < 70 (p = 0.38), Age > 70 (p = 0.38)
- Diarrhea: Age < 70 (p = 0.38), Age > 70 (p = 0.38)
- Nausea/Vomiting: Age < 70 (p = 0.38), Age > 70 (p = 0.38)
- 60 Day Mortality: Age < 70 (p = 0.38), Age > 70 (p = 0.38)
Conclusions

- Elderly patients benefit from FOLFOX4 treatment to a similar degree to younger patients.
- Elderly patients experience slightly more but manageable toxicity.
- Age alone should not be a criteria to exclude elderly patients from FOLFOX4 chemotherapy.

Caution

- Conclusions only applies to selected elderly patients for clinical trials.
- 2 of 4 trials limited eligibility to patients ≤ 75 years.
## Patient Age by Decade and Trial

<table>
<thead>
<tr>
<th>Age</th>
<th>A: MOSAIC</th>
<th>B: de Gramont</th>
<th>C: Goldberg</th>
<th>D: Rothenberg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of Patients</td>
<td>No. of Patients</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>≤ 39</td>
<td>126</td>
<td>12</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td>40-49</td>
<td>262</td>
<td>49</td>
<td>64</td>
<td>86</td>
</tr>
<tr>
<td>50-59</td>
<td>628</td>
<td>99</td>
<td>154</td>
<td>157</td>
</tr>
<tr>
<td>60-69</td>
<td>915</td>
<td>174</td>
<td>170</td>
<td>170</td>
</tr>
<tr>
<td>70-75</td>
<td>290</td>
<td>71</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>75-79</td>
<td>25</td>
<td>15</td>
<td>37</td>
<td>31</td>
</tr>
<tr>
<td>≥ 80</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

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OPTIMOX 1 Study design

A

FOLFOX4 until progression

B

FOLFOX7 x 6 cy
sLV5FU2 x 12 cy
FOLFOX7 x6 cy
Optimox 1 - Overall Survival

Patients >75 years vs Patients ≤ 75 years

- > 75 years: 20.7 months
- ≤ 75 years: 20.2 months

p = 0.15

Proportion vs weeks

0 25 50 75 100 125 150

0.0 0.2 0.4 0.6 0.8 1.0

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GERCOR
The Stop and GO Strategy
Optimox 2 Study

- 6 FOLFOX 7 mod → LV5 FU2 → Reintroduction of Folfox 7 if progression
- 6 FOLFOX 7 mod → Break → Reintroduction of Folfox 7 if progression

- n=202
- A RANDOMIZED PHASE II TRIAL

F. Maindrault-Goebel et al. ASCO 2007, Abstract 4013 actualisé
The Stop and GO Strategy
Optimox 2 Study

<table>
<thead>
<tr>
<th></th>
<th>Maintenance</th>
<th>Break</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>100</td>
<td>102</td>
<td>-</td>
</tr>
<tr>
<td>RR</td>
<td>63%</td>
<td>61%</td>
<td>NS</td>
</tr>
<tr>
<td>TDC (1)</td>
<td>10.8</td>
<td>9</td>
<td>0.32</td>
</tr>
<tr>
<td>CFI (2)</td>
<td>-</td>
<td>4.6</td>
<td>-</td>
</tr>
<tr>
<td>SG</td>
<td>24.6</td>
<td>18.9</td>
<td>0.05</td>
</tr>
</tbody>
</table>

- **Good Pronostic**
  - NA
  - 20.9

- **Poor Pronostic**
  - 28.7
  - 14.5

(1) Time to control disease
(2) Chemotherapy free interval

F. Maïndrault-Goebel et al. ASCO 2007, Abstract 1013 actualisé
Is it True in the Real Life?
Four Questions?

- What is the best Strategy: Monotherapy or Association?

- Folfox or Xelox: is Oral better than all infusion?

- Is there a place for targeted therapies with oxaliplatin in elderly?

- Treatment for which elderly population?
Monotherapy or Association?

- **FFCD (2000-05)- Preliminary result**
- **410 pts**
- **02/2002 – 02/2006**
- **Median Follow up : 25 months**
- **Advanced CRC with non resectable metastasis**
- **Arm A LV5FU2s ⇨ FOLFOX6 ⇨ FOLFIRI**
  Vs Arm B FOLFOX6 ⇨ FOLFIRI ⇨ other treatment
- **PFS 11.5 months VS 12 months**
- **OS 17 months vs 16 months**

Bouché et al ASCO 2007 abstract 4069
Monotherapy or Association?

- **FOCUS 2** a multicenter, 2×2 factorial randomized trial
- **460 patients**
- **Four arms:** (A) LV5FU2s, (B) FOLFOX, (C) Capecitabine et (D) Capox
- **Age:** <70 ans (101), 70-75 ans (161), >75 ans (198)
## FOCUS 2 Study

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>AB vs CD</th>
<th>AC vs BD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LV5FU2</td>
<td>FOLFOX</td>
<td>Cap.</td>
<td>CAPOX</td>
<td>FU vs cap</td>
<td>+/- oxali</td>
</tr>
<tr>
<td>↑ QOL at 12wk</td>
<td>60%</td>
<td>51%</td>
<td>64%</td>
<td>45%</td>
<td>56 vs 54% p=0,95</td>
<td>62 vs 48% p=0,03</td>
</tr>
<tr>
<td>RR at 12wk</td>
<td>16%</td>
<td>43%</td>
<td>17%</td>
<td>34%</td>
<td>p=0,66</td>
<td>p&lt;0,0001</td>
</tr>
<tr>
<td>PFS hazard ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR=0,92  p=0,41</td>
<td>HR=0,87  p=0,16</td>
</tr>
<tr>
<td>↑ dose at 6wk</td>
<td>51%</td>
<td>37%</td>
<td>41%</td>
<td>31%</td>
<td>P=0,14</td>
<td>P=0,02</td>
</tr>
<tr>
<td>Tox 3-4</td>
<td>24%</td>
<td>26%</td>
<td>36%</td>
<td>39%</td>
<td>P=0,008</td>
<td>P=0,09</td>
</tr>
</tbody>
</table>

Seymour MT ASCO 2007 n°9030

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# The Backbone of treatment for Advanced CRC

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treatment strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver and/or lung metastases only and resection might be possible after chemotherapy</td>
<td>3 drug combination</td>
</tr>
<tr>
<td>Poor perfomans status or aggressive disease or imminent or present tumor related symptoms</td>
<td>3 (or2) drug combination</td>
</tr>
<tr>
<td>Multiple metastases and good to moderate performance status and less aggressive disease or comorbid conditions</td>
<td>Single agent fluorouracil (+/-bevacizumab ?)</td>
</tr>
</tbody>
</table>

HJ Schmoll and D Sargent – Lancet 2007;370-105-107
 FolFox or Xelox ?

- GERICO II : Impact of Xelox regimen on independance of elderly patients measured by ADL
- 60 patients >70 YEARS (Median age: 78 years old)
- Advanced CCR first line
- Treatment: Capecitabine 750 mg/m² orally bid d1-14 + oxaliplatin 90 mg/m² IV q3w
- No ADL decrease after 3 courses
- No ADL decrease after 6 courses in 96% of patients
- OR: 33%, stabilisation: 18%
- Toxicity grade 3-4: haematological 12%, diarrhea 13%, hand-foot syndrome 0% (19% grade 1-2), neurotoxicity 2% (67% grade 1-2)

Viret F ASCO 2007 n°19513 (non sélectionné)
Xelox as first-Line treatment for elderly

- Phase II Trial – 50 patients
- From January 2003 to September 2003
- Mean age: 76 years
- 28 pts had comorbidities
- ORR: 36%
- OS: 13.2 months
- 12 patients received a second line
- « A good therapeutic option in the elderly »

J Feliu et al Br J of Cancer 2006;94,969-975
**FUFOX vs CAPOX**

- **From August 2002 to August 2004** 476 patients were randomized
- 140 patients >70 year-old
- CRC metastatic first-line
- OR : >70 years vs <70 years : 49 vs 52%
- PFS : >70 years vs <70 years : 7,7 vs 7,5 months (OR: 1,07; IC95% 0,86-1,34)
- OS : >70 years vs <70 years : 14,4 vs 18,8 months (OR: 1,37; IC95% 1,07-1,76 p=0,013)
- Tox 3-4 : >70 years more GI adverse effects and less neurosensory toxicity

<table>
<thead>
<tr>
<th></th>
<th>FUFOX</th>
<th>CAPOX</th>
<th>Odd Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>&gt; 70 years</td>
<td>7,9 months</td>
<td>7,6 months</td>
</tr>
<tr>
<td>OS</td>
<td>&gt; 70 years</td>
<td>14,4 months</td>
<td>14,2 months</td>
</tr>
<tr>
<td>ORR</td>
<td>&gt; 70 years</td>
<td>54%</td>
<td>46%</td>
</tr>
</tbody>
</table>
5-FU vs Capecitabine Preference Trial

First treatment course

- Capecitabine
- i.v. 5-FU/LV

Second treatment course

- i.v. 5-FU/LV
- Capecitabine

R = randomisation; Q = questionnaire

Gollins SW, Samuel L, Napier M and Twelves C. European Society of Medical Oncology Meeting 2004, Annals of Oncology 15, Sup 3, abst 347
Overall patient preference before and after treatment

- All patients (n=94)
  - Before: 79, After: 58
  - Oral: 58, Oral preference: 79%
  - I.V.: 4, I.V. preference: 58%
- Oral → i.v. (n=51)
  - Before: 82, After: 58
  - Oral: 58, Oral preference: 82%
  - I.V.: 6, I.V. preference: 58%
- I.V. → Oral (n=43)
  - Before: 72, After: 57
  - Oral: 57, Oral preference: 72%
  - I.V.: 2, I.V. preference: 29%
HOW MANY COLORECTAL CANCER (CRC) PATIENTS OLDER THAN 70 YEARS MAY BE SAFELY TREATED WITH BEVACIZUMAB?

- From January 2004 to December 2005
- 91 pts > 70 years - Median age 76 years old
- 65 pts had comorbidities: (CIRGS)
  - 29/91 comorbidities grade >2
  - 36/91 Comorbidities grade 1
  - 26/91 no comorbidity
    - Bevacizumab is contraindicated for 36% of pts
    - It’s moot for 40% of patients
    - 34% of patients could benefit of bevacizumab

L. M. Pasetto ASCO 2006, abstract 13589
# Bevacizumab after 75 years old: Caution!

<table>
<thead>
<tr>
<th>Toxicity grade 3-4</th>
<th>Median age</th>
<th>65-69</th>
<th>70-74</th>
<th>≥75</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>19</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Arterial thromboembolic events</td>
<td>10%</td>
<td>11%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Venous thromboembolic events</td>
<td></td>
<td></td>
<td><strong>11.6%</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10%</td>
<td>11%</td>
<td><strong>29%</strong></td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td>0%</td>
<td>5%</td>
<td><strong>5%</strong></td>
<td></td>
</tr>
</tbody>
</table>

Median age: 65-69, 70-74, ≥75

Raman AK, ASCO 2007 n°14546
Madrid - VIII e SIOG -
GERICO 08 : Xelox
Bevacizumab in Elderly

Dr Frédérique ROUSSEAU  IPC-Marseille
BECT-FNCLCC

XELOX – Avastin® 6 cures
Capecitabine  750 mg/m² PO bid J1-14
Oxaliplatin  90 mg/m² IV  J1
Bevacizumab  7.5 mg/m² IV  J1

Aims : Study the feasibility of the combination With XELOX-Avastin®

ORR
PFS
OS
Toxicity
Impact of independance measured by ADL

70 patients

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Who can profit of the treatment?
CGA: Help for Oncologist

Algorithm used in decision making of older-aged patients with cancer.

Balducci L Cancer Control. 2007;14:7-12
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### Cognitive functions

1. Date du jour et nom de la ville de l'Hôpital
2. Répétition de trois mots (cigare, fleur, porte ou citron, clé, ballon) et après quelques minutes

### Dependance

3. Aide pour :
   - téléphoner
   - faire les courses
   - préparer les repas
   - entretenir la maison
4. Appui monopodal 5s

### Comorbidities

1. Hospitalisation dans l'année précédente
2. Poly médications > 5
6. Poly médications > 5

### Renal function and nutritial status

7. Clairance de la créatinine >30ml/mn
8. Albuminémie >30g/l

### Depression and helper

9. Vous sentez vous souvent triste ou déprimé ?
10. Présence de l'Entourage*

*Aidant ou famille*