Relapsed Ovarian Cancer

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OVCA in elderly patients

- Pts $\geq 65$ years = 48 % in US
- Peak incidence between 75 and 80 years
- More advanced stages (FIGO III C and IV)
- Less radical surgery
- Bulky residual disease more frequently
- Chemotherapy feasible
- Underrepresentation in clinical trials
Hutchins et al.
Underrepresentation of patients 65 years of age or older in cancer- treatment trials.
1st L Chemotherapy: is CbP the standard?

• AGO – OVAR phase III study – Retrospective subgroup analysis
  103 pts (13 %) > 70 years old (Med. 73.5 years)
  Chemo received / planned dose, tolerance and QoL: NO DIFFERENCE except
  ▶ febrile neutropenia: 5 % vs 1 % (p < 0.001)
  ▶ early treatment discontinuation


• COHORT STUDY at the MSKCC
  108 pts (37 %) > 65 years old.
  No effect of age on treatment tolerance, PFS and OS

  Gynecol Oncol. 2007 Aug;106(2):381-7
1st L Chemotherapy : is CbP the standard ?

Pooled analysis of 2 consecutive phase II GINECO studies – nb= 155 pts

**Multicentric, specific, few exclusion criteria**

<table>
<thead>
<tr>
<th></th>
<th>Cb C trial</th>
<th>Cb P trial</th>
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<tbody>
<tr>
<td>Median age</td>
<td>76 [70 – 90]</td>
<td>75 [70 – 89]</td>
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<tr>
<td>PS 0-1 / 2-3 (%)</td>
<td>56 / 44</td>
<td>74 / 26 [p = 0.08]</td>
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<td>Optimal surgery (%)</td>
<td>21</td>
<td>41 [p = 0.03]</td>
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<tr>
<td>Serous histology (%)</td>
<td>73</td>
<td>71</td>
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<tr>
<td>Stage III / IV (%)</td>
<td>76 / 24</td>
<td>78 / 22</td>
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<tr>
<td>Ascites (%)</td>
<td>59</td>
<td>69</td>
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<tr>
<td>0 – 3 drugs daily</td>
<td>45</td>
<td>65 [p = 0.03]</td>
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</tbody>
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Tredan, Freyer et al, Annals of Oncology 2007, 18: 256-262

BETTER, BUT...
1st L Chemotherapy: is CbP the standard?

Overall survival of 2 consecutive phase II GINECO studies

Multivariate analysis:
Paclitaxel use = poor prognostic factor
HR = 2.42, p = 0.01
1st L Chemotherapy: prognostic factors

Multivariate analysis: poorer survival

- Stage IV: HR = 3.05 - p = 0.001
- Paclitaxel: HR = 2.42 - p = 0.01
- Depression: HR = 5.11 - p < 0.001
- Lymphopenia: HR = 4.68 - p = 0.006

Figure 1. Kaplan–Meier estimates of (A) progression-free survival, (B) overall survival and (C) overall survival according to the presence of zero, one, or two or more prognostic factors (i.e., symptoms of depression, more than six comediations per day, FIGO stage IV).


Figure 2. Kaplan–Meier estimates of overall survival of patients receiving carboplatin and paclitaxel according to the total Hospital Anxiety and Depression Scale (HADS) score: —, total HADS <15 (number of patients = 26); ---, total HADS ≥15 (number of patients = 16).
1st L Chemotherapy: the GINECO «Elderly – Carboplatin» trial (completed end 2009)

Med Age 78 years (70 – 93)
- ≥ 80 years: 45/111 (40.5%)
- PS ≥ 2: 48/111 (43.2%)
- Depression: 20/111 (18.0%)
- ≥ 4 drugs / day: 76/111 (68.5%)
- ADL dependence: 61/111 (55%)
- IADL dependence: 83/111 (74.8%)

Measure of telomere length (frailty)
Psychometric / psychological evaluation

Carbo trial: 2007 – 2009 – 111 pts
1st L. Chemotherapy: EWOC trial (in preparation)

• EWOC = Elderly Women Ovarian Cancer
• International prospective clinical trial (GINECO + GCIG)
• Randomized phase II
  – Arm A = Carbo AUC 5 + Pacli 135 mg/sqm
  – Arm B = Carbo AUC 5
  – Arm C = weekly Carbo AUC 2 + Pacli 60 mg/sqm (MITO protocol)
RELAPSE in OVCA: epidemiology

- 75% of recurrence after 1st L. CT (10% per year in pCR)
- Median TTP after 1st L. CT = 16 to 22 months
- Median time of survival after recurrence of 2 years
- Prognostic factors of relapse:
  - pCR after 1st L. CT
  - Histological type
- Prognostic factor after relapse = length of free interval without CT
RELAPSE in OVCA

- Retrospective study of GINECO phase II/III studies (nb = 583 pts)

- Objective:
  - Impact of free interval on overall survival

E. Pujade-Lauraine - Proc. ASCO 2002
RELAPSE in OVCA:
Guidelines of the NICE
(National Institute for Clinical Excellence)

1st L Paclitaxel-Carboplatin

Sensible
(> 12 months)

Partially sensible
(6-12 months)

Resistant/Refractory
(< 6 months)

Paclitaxel-Carboplatin
Caelyx®-Carboplatin

Paclitaxel-Carboplatin
CAELYX® mono
Yondelis®-Caelyx®

Paclitaxel mono(weekly ++)
CAELYX® mono
Topotecan

NHS. Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer. Guidance 28, 45 and 55. Mai 2005
Pegylated liposomal doxorubicin and carboplatin versus paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients:

Treatment at recurrence and overall survival final analysis from CALYPSO phase III GCIG trial

Marth et al. J Clin Oncol 2011;29 (suppl; abstr 5052)
Background

CALYPSO is a large international randomized phase III trial comparing C-PLD and C-P in pts with OC in late relapse.

• From 04/05 to 09/07, 976 eligible pts were randomized to either C-P (carboplatin AUC 5 iv d1 + paclitaxel [P] 175 mg/m² 3h iv d1, q3w) or C-PLD (Carboplatin + PLD 30 mg/m² iv d1 q4w) for at least 6 cycles.

• Results of the progression-free survival (PFS), the primary endpoint, show a benefit in pts treated with C-PLD with a hazard ratio (HR) of 0.82 (P = .005)\(^1\).

• Overall severe non-hematologic toxicity (36.8% v 28.4%; \(P < .01\)) including alopecia, neurotoxicity and carboplatin hypersensitivity leading to early discontinuation (15% v 6%; \(P < .001\)) – occurred more frequently in the C-P arm

• It was explored whether the treatment effect on PFS recently observed in CALYPSO was maintained after further treatment. OS of pts was analysed.

Patients were followed for 49 months (range 0-68 mo)

CALYPSO: Study design

International, Intergroup, Open-label, Randomized Phase III Study

Ovarian cancer in late relapse (> 6 months) after 1st- or 2nd-line platinum-based therapy (previous taxane required)

Stratification:
• Therapy-free interval (6-12 mo vs > 12 mo)
• Measurable disease (yes vs no)
• Center

Experimental arm: CD
PLD 30 mg/m² IV d 1
Carboplatin AUC 5 d 1

Control arm: CP
Paclitaxel 175 mg/m² IV d 1
Carboplatin AUC 5 d 1

Overall Survival

Median OS
30.7 (C-PLD) vs 33.0 (C-P) months
HR 0.994, (95% CI 0.85-1.16); p=0.937

logRank = 0.937

Therapy fee interval (6-12 m vs >12m) (p<0.001), ECOG performance status 0 vs >1 (p<0.001) ; CA125 <100 vs >100 (p<0.001), measurable disease No vs <50mm (p =0.021) vs >50mm (p<0.001), and number of disease sites one vs >1 (p = 0.014) were found as independent prognostic factors for OS
Most patients (70%) received 2 or more lines of chemotherapy after Calypso treatment.
The number of patients who received PLD in C-P arm (68%) was significantly higher (p<0.001) than the number of patients who received paclitaxel in the C-PLD arm (43%)
Elderly patients in CALYPSO study

- 157 pts (= 16 %) > 70 years old
- Median age = 73 years old (70-82 y)
- PS <= 2
- Tolerance = no difference except neurotoxicity grade ≥ 2 (24.7 % vs 15.6 %, p = 0.006)
- Efficacy = no difference

▷ Contra-indication of Paclitaxel use
▷ How can we manage PLD stock rupture?
CONCLUSIONS

• OVCA is a chemosensitive but not a chemocurative disease
• Effectiveness of relapse treatments but not lasting
• Dramatic underrepresentation of elderly patients in clinical trials

➢ Urgence to enrolle 5 % and more of patients ≥ 75 years old in specific clinical trials conformed to INCa recommandation (National Institute of Cancer, France) with the support of SoFOG (French Society of Geriatric Oncology)