Final overall survival results of phase III GCIG CALYPSO trial of pegylated liposomal doxorubicin and carboplatin vs paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients

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BACKGROUND: The CALYPSO phase III trial compared CD (carboplatin-pegylated liposomal doxorubicin (PLD)) with CP (carboplatin-paclitaxel) in patients with platinum-sensitive recurrent ovarian cancer (ROC). Overall survival (OS) data are now mature.

METHODS: Women with ROC relapsing >6 months after first- or second-line therapy were randomised to CD or CP for six cycles in this international, open-label, non-inferiority trial. The primary endpoint was progression-free survival. The OS analysis is presented here.

RESULTS: A total of 976 patients were randomised (467 to CD and 509 to CP). With a median follow-up of 49 months, no statistically significant difference was observed between arms in OS (hazard ratio = 0.99 (95% confidence interval 0.85, 1.16); log-rank P = 0.94). Median survival times were 30.7 months (CD) and 33.0 months (CP). No statistically significant difference in OS was observed between arms in predetermined subgroups according to age, body mass index, treatment-free interval, measurable disease, number of lines of prior chemotherapy, or performance status. Post-study cross-over was imbalanced between arms, with a greater proportion of patients randomised to CP receiving post-study PLD (68%) than patients randomised to CD receiving post-study paclitaxel (43%; P < 0.001).

CONCLUSION: Carboplatin-PLD led to delayed progression and similar OS compared with carboplatin-paclitaxel in platinum-sensitive ROC.

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In patients with recurrent ovarian cancer (ROC) that is platinum-sensitive (relapsing >6 months following prior treatment), an analysis of International Collaborative Ovarian Neoplasm (ICON) and Arbeitsgemeinschaft Gynäkologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) phase III trials demonstrated improved overall survival (OS) with paclitaxel-carboplatin combination chemotherapy compared with carboplatin alone (hazard ratio (HR), 0.82; 95% confidence interval (CI), 0.69–0.97; P = 0.02) (Parmar et al, 2003; Pfisterer et al, 2006). In a phase II trial of similar design, González-Martín et al (2005) also showed prolonged survival with paclitaxel-carboplatin (HR 0.31; 95% CI, 0.14, 0.68; P = 0.0021). However, this combination is accompanied by a significant toxicity, including peripheral neuropathy, neutropenia, and alopecia. Furthermore, additional survival improvement for this patient population remains an important goal, with a 2-year survival rate of 57% observed in the paclitaxel-carboplatin arm of the ICON/AGO-OVAR trials. Pegylated liposomal doxorubicin (PLD) has been shown an active drug in platinum-sensitive ROC and has a better toxicity profile than paclitaxel. An earlier study evaluating PLD monotherapy vs topotecan demonstrated significantly improved progression-free survival (PFS) and OS in patients receiving PLD (Gordon et al, 2001, 2004). The survival benefit was more pronounced for patients with partially sensitive ROC (treatment-free interval (TFI) of >6 months and <12 months). In these patients, the HR for OS was 1.58 compared with 1.15 for those with...
a TFI > 12 months (Gordon et al., 2004). The Groupe d’Investigateurs Nationaux pour l’Etude des Cancers Ovariens et du sein (GINECO) has explored the combination of PLD and carboplatin in a phase II trial. The OS was 21 months in patients with partially platinum sensitive ROC and 36 months in fully sensitive ROC (Ferrero et al., 2007). Using the same regimen in a prospective, consecutive cohort, an OS of 30 months was observed in 32 partially sensitive patients and 54 months in 49 fully sensitive patients (Weber et al., 2010).

CALYPSO, a large international randomised Gynecologic Cancer Intergroup (GCIG) phase III trial, compared PLD plus carboplatin (CD) to paclitaxel plus carboplatin (CP) in 976 patients with platinum-sensitive ROC (Pujade-lauraine et al., 2010). The primary endpoint was the non-inferiority of CD relative to CP in PFS. Patients receiving CD experienced a statistically significant improvement in PFS compared with patients receiving CP (HR = 0.82 (95% CI, 0.72, 0.94); P = 0.005). Overall severe non-haematologic toxicity (28.4% vs 36.8%; P = 0.001) occurred less frequently in the CD arm, making this regimen an attractive option with a favourable therapeutic index for patients with platinum-sensitive ROC.

Overall survival data are now mature from CALYPSO. The current analysis investigates whether the observed PFS improvement translated into an OS benefit for patients receiving CD compared with CP for platinum-sensitive ROC.

PATIENTS AND METHODS

The patients, methods, and design of CALYPSO were previously reported (Pujade-lauraine et al., 2010). Briefly, patients had ovarian cancer that recurred > 6 months after first- or second-line platinum-based chemotherapy and had received a taxane. Treatment consisted of carboplatin (C) AUC 5 plus PLD 30 mg m⁻² (CD) on day 1 every 4 weeks or C AUC 5 plus paclitaxel (P) 175 mg m⁻² (CP) on day 1 every 3 weeks. Patients received six cycles in the absence of disease progression or unacceptable toxicity, with additional cycles allowed for patients experiencing response or stable disease.

Randomisation and masking

CALYPSO was an international randomised, phase III, open-label, multicenter trial. Randomisation was performed in permuted blocks with stratification by measurable disease (yes vs no), TFI from last chemotherapy (6–12 vs > 12 months), and centre.

Statistical analysis

The study design was that of non-inferiority for PFS. The secondary endpoint was OS and analysed using a log-rank test. Exploratory analysis of baseline characteristics was performed with Cox regression and pre-specified subgroups were assessed for differing treatment effects.

RESULTS

A total of 976 patients were randomised between April 2005 and September 2007 (467 to CD and 509 to CP). Baseline patient and disease characteristics were balanced between arms (Table 1). The majority of patients had FIGO stage III/IV disease and had received only one line of prior treatment. Two-thirds of the patients had a TFI of > 12 months since prior chemotherapy. Further details of patient characteristics are reported elsewhere (Pujade-lauraine et al., 2010).

In a prior analysis, PFS was statistically significantly prolonged in the CD arm (HR = 0.82 (95% CI, 0.72, 0.94); P = 0.005) based on a median follow-up of 22 months (Pujade-lauraine et al., 2010). Median PFS times were 9.4 months in the CP arm and 11.3 months in the CD arm.

In this analysis, the median follow-up is 49 months (range 0–68 months) with a total of 663 deaths: 346 in the CP arm and 317 in the CD arm. The hazard ratio for CP : CD was 0.99 (95% CI, 0.85, 1.16), which was not statistically significant (log-rank P = 0.94; Figure 1). Median survival times were 30.7 months in the CD arm and 33.0 months in the CP arm.

Post-study therapy was received by 90% of patients in either arm of CALYPSO. The majority of patients (69%) received two or more lines (Table 2). Analysis of cross-over between the arms demonstrated an imbalance. The proportion of patients randomised to CP who received PLD as post-study therapy (68%) was higher than the proportion of patients randomised to CD who received paclitaxel as post-study therapy (43%; P < 0.001).

Factors that significantly correlate to survival were age, TFI, ECOG PS, residual disease, CA125, measurable disease, longest lesion size, and disease site in univariate analyses. In multivariate analysis, TFI > 12 months, ECOG PS 0, CA125 < 100 U ml⁻¹, non-measurable disease, and one involved disease site remained significantly correlated to survival (Table 3).

For a priori subgroups age, body mass index, TFI, measurable disease, number of lines of prior chemotherapy, and ECOG performance status, univariate proportional hazards regression for treatment did not show any statistically significant effect (Table 4).

DISCUSSION

CALYPSO is the largest clinical trial in ROC, enrolling 976 patients. Designed as a non-inferiority trial, CALYPSO demonstrated that

### Table 1. Baseline characteristics

| Characteristic                        | CD             | CP             |
|---------------------------------------|----------------|----------------|
| Median age, years                     | 60.5 (n = 466) | 61.0 (n = 509) |
| ECOG performance status              |                |                |
| 0                                     | 286 (61)       | 317 (62)       |
| 1                                     | 159 (34)       | 164 (32)       |
| 2                                     | 13 (3)         | 15 (3)         |
| Primary disease site ovarian          |                |                |
| Papillary/serous histology            | 415 (89)       | 451 (89)       |
| Initial FIGO stage                    |                |                |
| III                                   | 52 (11)        | 59 (12)        |
| III/IV                                | 401 (86)       | 427 (84)       |
| Number of previous therapy lines     |                |                |
| 1                                     | 408 (88)       | 421 (83)       |
| 2                                     | 58 (12)        | 87 (17)        |
| Prior taxane                          | 462 (99)       | 500 (99)       |
| Median interval since prior therapy   |                |                |
| 6–12 months                           | 162 (35)       | 182 (36)       |
| > 12 months                           | 304 (65)       | 326 (64)       |
| Measurable disease                    |                |                |
| Yes                                   | 281 (60)       | 321 (63)       |
| No                                    | 185 (39)       | 188 (37)       |
| Turnover size                         |                |                |
| < 5 cm                                | 377 (81)       | 419 (82)       |
| ≥ 5 cm                                | 89 (19)        | 90 (18)        |
| Number of sites of recurrence        |                |                |
| 1                                     | 217 (47)       | 245 (48)       |
| > 1                                   | 249 (53)       | 264 (52)       |

Abbreviations: CD = carboplatin-pegylated liposomal doxorubicin; CP = carboplatin-paclitaxel; ECOG = Eastern Cooperative Oncology Group. *Missing values to attain 100%.
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CD was not only non-inferior to CP in PFS but was also superior (HR = 0.82, P = 0.005) in patients with platinum-sensitive ROC. Furthermore, CD was associated with less carboplatin hyper-sensitivity, peripheral neuropathy, prolonged neutropenia, and alopecia. Toxicities observed more commonly with CP were mucositis, nausea and vomiting, and palmar-plantar erythrodysesthesis. These toxicities were generally low-grade, short-term, and manageable (Pujade-Lauraine et al, 2010; Joly et al, 2011). Taken together, CD emerged as a welcome option for treating platinum-sensitive ROC that exhibited a favourable therapeutic index.

Several analyses of CALYPSO have been undertaken (Gladieff et al, 2011; Joly et al, 2011; Kurtz et al, 2011; Lee et al, 2011). In the current analysis, OS of CD and CP were evaluated. In the overall population, OS was similar between arms (HR = 0.94). Median survival was 30.7 months in the CD arm. Prior investigations of this regimen have shown median survival times of 25–39 months (Ferrero et al, 2007; Weber et al, 2009; Bafaloukos et al, 2010). Median survival in the CP arm was 33.0 months; when analysed by patient subgroups according to age, BMI, TFI, measurable disease, number of prior therapy lines, and ECOG PS, no statistically significant differences emerged between treatment arms in any of the subgroups. Notable was the lack of difference between arms regardless of TFI. The HR for OS in the partially platinum-sensitive subgroup (TFI 6–12 months) was 1.01 (95% CI, 0.80, 1.28; P = 0.92), whereas the HR for OS in the sensitive subgroup (TFI > 12 months) was 0.99 (95% CI, 0.81, 1.21; P = 0.90). These results lie in contrast to the study of monotherapy

Figure 1 Overall survival in patients receiving carboplatin-paclitaxel or carboplatin-PLD for platinum-sensitive recurrent ovarian cancer. Abbreviation: PLD, pegylated liposomal doxorubicin.

Table 2 Number of post-study therapy lines and cross-overs

| Treatment             | Number of lines | Patients (%) |
|-----------------------|-----------------|--------------|
|                      | 0               | 10           |
|                      | 1               | 21           |
|                      | 2               | 25           |
|                      | 3               | 21           |
|                      | 4               | 13           |
|                      | 5–11            | 10           |
|                      | 2 or more lines | 69           |

Cross-overs

CP arm 68
CD arm 43

Table 3 Multivariate cox regression model of overall survival (N = 959)

| Factors          | N    | HR   | 95% CI   | P-value |
|------------------|------|------|----------|---------|
| TFI, months      |      |      |          |         |
| 6–12             | 342  | 0.50 | 0.43, 0.59| <0.001  |
| ≥12              | 617  | 0.50 | 0.43, 0.59| <0.001  |
| ECOG PS          |      |      |          |         |
| 0<1              | 344  | 1.37 | 1.17, 1.60| <0.001  |
| ≥1               | 615  | 1.37 | 1.17, 1.60| <0.001  |
| CA125, U/ml      |      |      |          |         |
| <100             | 316  | 1.78 | 1.49, 2.14| <0.001  |
| ≥100             | 643  | 1.78 | 1.49, 2.14| <0.001  |
| Measurable disease/longest lesion, mm |      |      |          |         |
| ≤50              | 422  | 1.28 | 1.04, 1.57| 0.02    |
| >50              | 176  | 1.78 | 1.40, 2.26| <0.001  |
| Involved disease sites |      |      |          |         |
| 1                | 453  | 1.26 | 1.05, 1.52| 0.014   |
| >1               | 506  | 1.26 | 1.05, 1.52| 0.014   |

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; TFI = treatment-free interval. *This category includes any unknown or not applicable values.

Table 4 Overall survival by treatment arm in pre-defined patient subgroups

|               | N | Univariate cox regression model |
|---------------|---|---------------------------------|
|               |   | CD CP HR 95% CI Subgroup P-value Interaction P-value |
| Age, years    |   |                                 |
| <70           | 395 423 | 0.98 0.83, 1.16 0.80 0.61 |
| ≥70           | 71   86  | 1.10 0.76, 1.58 0.62 |
| BMI, kg m⁻²   |   |                                 |
| <30           | 378 399 | 1.00 0.85, 1.19 0.98 0.74 |
| ≥30           | 88   110 | 0.95 0.67, 1.35 0.76 |
| TFI, months   |   |                                 |
| 6–12          | 161 | 183 1.01 0.80, 1.28 0.92 0.86 |
| ≥12           | 305 326 | 0.99 0.81, 1.21 0.90 |
| Measurable disease | No 137 138 | 0.88 0.65, 1.21 0.56 0.31 |
|               | Yes 329 371 | 1.07 0.90, 1.27 0.47 |
| Number of prior lines | 1 408 418 | 0.99 0.84, 1.17 0.92 0.98 |
|               | ≥2 58 88   | 0.97 0.65, 1.46 0.74 |
| ECOG PS       |   |                                 |
| 0             | 295 329 | 0.99 0.81, 1.20 0.92 0.95 |
| ≥1            | 171 180 | 0.99 0.78, 1.27 0.95 |

Abbreviations: BMI = body mass index; CD = carboplatin-pegylated liposomal doxorubicin; CP = carboplatin-paclitaxel; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; TFI = treatment-free interval. *Interaction test is the P-value associated with the interaction term in the Cox regression model containing treatment effect, subgroup variable, and their interaction.
PLD vs topotecan, which showed a more pronounced survival benefit for PLD relative to topotecan in patients with partially platinum-sensitive disease (Gordon et al., 2004). An imbalance in post-study therapy may have affected OS and mitigated the PFS benefit observed with CD. Post-study PLD was received by 68% of patients in the CP arm, while post-study paclitaxel was administered to 43% of patients in the CD arm (P < 0.001).

The results of CALYPSO demonstrate that carboplatin-PLD offers an attractive option as compared with the standard of care, carboplatin-paclitaxel, for the treatment of platinum-sensitive ROC. Patients receiving carboplatin-PLD experienced delayed progression, similar survival, less carboplatin hypersensitivity, and less peripheral neuropathy, a toxicity associated with long-term sequelae, compared with patients receiving carboplatin-paclitaxel.

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Conflict of interest

The authors declare no conflict of interest.

Participant Institutions

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