Published in final edited form as:

Expert Rev Pharmacoecon Outcomes Res. 2012 June ; 12(3): 279–281. doi:10.1586/erp.12.22.

Quality-of-life results used to endorse changes in standard of care for recurrent platinum-sensitive ovarian cancer

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Abstract

Most women with ovarian cancer will suffer a recurrence. Unfortunately, although initial treatment can lead to undetectable disease, recurrent disease is often more challenging to control. As curative intent is less common after relapse, patients and doctors argue for improving quality-of-life (QoL) outcomes when therapies are selected. The article reviewed here discusses the QoL results of a trial in platinum-sensitive recurrent ovarian cancer where over 900 patients were randomized to the standard treatment (carboplatin and paclitaxel) versus carboplatin and pegylated liposomal doxorubicin. In the paper under evaluation, the standard of care is challenged based on a favorable clinical outcome in addition to QoL results in the experimental arm.

Keywords

pegylated liposomal doxorubicin; quality of life; recurrent ovarian cancer

The majority of women with ovarian cancer present with advanced-stage disease. Despite the often aggressive presentation of the disease, a complete response to surgery and platinum/taxane chemotherapy is most frequently encountered. Unfortunately, most patients will suffer a recurrence, and treatment of recurrent ovarian cancer is often less successful. It is known, however, that women with a greater than 6-month platinum-free interval may be re-treated with a platinum and taxane combination, as they are labeled 'platinum-sensitive.' This paradigm has been interpreted as the 'standard of care' in this setting has been to retreat with carboplatin and paclitaxel (CP). In 2005, the CALYPSO trial was developed to address alternative therapies for these women [1,2]. This trial examined the use of carboplatin and pegylated liposomal doxorubicin (CD) as at least a noninferior and safe alternative to CP. As it was a noninferiority study, its large sample size caused it to be overpowered to detect small and potentially clinically insignificant differences in progression-free survival (PFS). Indeed, the improved PFS seen in this study did not translate into an improvement in overall

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Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

survival. This was not surprising, as the difference in PFS was small and crossover was common [3]. These details make patient-reported outcomes one of the most important metrics in this trial.

As the likelihood for cure is diminished in recurrent ovarian cancer treatment, many have suggested that quality-of-life (QoL) outcomes should be pursued. Brundage *et al.* [1] thus report on the QoL results from the CALYPSO trial to further advocate for taxane-free alternatives to treat these women. Frequently suggested is the important relationship between poorer physical wellbeing and risk of death in multiple cancer types, including ovarian cancer [4]. Certainly, the CP combination is associated with detriments in physical functioning, including fatigue, nausea and side effects from treatment, such as neuropathy, all of which are measured by the physical wellbeing subscale. Many of the symptoms are known to be long-lasting beyond the completion of therapy. For example, in a recent article by Grover *et al.*, over 60% of ovarian cancer survivors reported peripheral neuropathy as a late effect of treatment [5]. Thus, with the endorsement of a new alternative to the standard of care in recurrent ovarian cancer, QoL outcomes are necessary to report on prior to supporting therapies, despite possible improvements in therapeutic indices.

Summary of methods & results from the paper

In the CALYPSO trial, Pujade-Lauraine *et al.* randomly assigned 976 patients to CD (n = 467) versus CP (n = 509). In this trial, pegylated liposomal doxorubicin was dosed at 30 mg/m² on day 1 and given at 28-day intervals, while paclitaxel was dosed at 175 mg/m² and given at 21-day intervals [2]. Carboplatin was given an area under the curve of 5 every 21 days on both arms [2]. Patients were enrolled if they were at least 6-month progression-free from their initial first- or second-line platinum-based chemotherapy regimen; however, previous taxane therapy was required. This study was designed as a noninferiority trial with PFS as the end point. Toxicity was measured by the National Cancer Institute-Common Toxicity Criteria for adverse events (version 3.0), and all patients were given the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 instrument (a patient-reported QoL measurement tool) to complete at randomization (baseline) and at 3-, 6-, 9- and 12-month intervals.

The PFS and toxicity data for the CALYPSO trial were previously reported [2]. Overall, the PFS for the CD arm was statistically superior to the CP arm (hazard ratio: 0.821; 95% CI: 0.72–0.94; p = 0.005). Interestingly, discontinuation of study owing to severe nonhematologic toxicity occurred more frequently in the CP arm (p < 0.001). Grade 2 or higher alopecia, hypersensitivity reactions and sensory neuropathy were all more common in the CP arm, although more hand–foot syndrome, nausea and mucositis were present in the CD arm. Owing to these differences, it was important to document the patient-reported outcomes (QoL) so as to explain in greater detail the effect of these toxicities on QoL in order to further support the use of CD in these patients.

The QoL data were reported as mean change scores at each time point compared with baseline scores. Brundage *et al.* defined a minimal important difference of ten points (on a 100-point scale) as a clinically significant change in QoL [1]. If patients had a decrease of

greater than or equal to ten points, then their QoL was described as ‘worsened’, whereas if they had an increase of greater than or equal to ten points then their QoL was described as ‘improved’. Approximately 90% of patients enrolled on this trial completed baseline QoL assessments. The completion of patient-reported QoL assessments decreased at each time point, with approximately 75% completing the assessments at 3 months, 60% at 6 months, and 50% at 9 and 12 months. Despite the fact that only approximately 80% of patients had baseline plus one other QoL data point available for analysis, this was not statistically significant between the two arms. Furthermore, using a multivariate analysis, there were no significant associations between these missing data and such patient characteristics as therapy-free interval, cancer antigen 125, treatment, measurable disease and involved disease sites.

Although there were statistically significant differences in physical functioning and global QoL scores between baseline and 3 months, with CP having worse scores, these differences were still described as ‘modest’ (between 3- and 5-point differences), and were not appreciated at the 6-month measurement time. However, when looking at symptom-specific questioning, patients treated with CP had long-lasting significant reports of peripheral neuropathy, more chemotherapy side effects in general and worse body image (still present at the 6-month intake; $p < 0.02$). Interestingly, those on CP reported less impact of therapy on sexual functioning and nausea/vomiting. The individual symptom complaints and their different incidences within the two arms were not well reflected in the subscale or global QoL scores.

An interesting subanalysis described within this article discusses the presence of patient-reported abdominal discomfort compared with measureable disease status. Approximately 40% of patients enrolled on this trial had no measurable disease at the time of randomization. Despite the nonmeasurable disease, approximately 50% of patients still reported abdominal pain and gastrointestinal symptoms on the ovarian cancer subscale tool (42% with scores between 1 and 30 and 48% with scores greater than 30). Although not significantly different between the CP and CD arms, most patients (even those with symptom scores above 30) demonstrated improvement in abdominal discomfort and gastrointestinal symptoms scores over time.

Discussion

Pujade-Lauraine *et al.* [2] and Brundage *et al.* [1] should be commended for their interesting data regarding the use of CD in platinum-sensitive ovarian cancer patients. These authors demonstrate the importance and utility of QoL data to the challenge standard of care in large randomized Phase III trials. In challenging the standard of care, they have found improvement not only in clinical outcomes but also in QoL scores for women treated with CD. In the treatment of recurrent disease, where survival can be limited, QoL improvements during known toxic therapy is an important consideration. In addition, CP was associated with more physician-reported toxicities, such as alopecia and hypersensitivity, compared with CD. Finally, the every-4-week schedule of CD is an obvious advantage over the every-3-week schedule of CP administration.

Five-year view

With the QoL improvements seen in several areas for patients treated with CD, Brundage *et al.* highlight the finding that neither fatigue nor attitude/concern scores were significantly affected (improved) with therapy [1]. As fatigue is the most common and often the most concerning side effect with cancer therapy, this needs to be addressed in prospective symptom management trials [6]. In addition, this study emphasizes the fact that QoL measurement is the only trial end point available to measure the benefits of disease progression delay and symptom control, thus supporting treatment for at least a palliative care benefit in the recurrent setting. The incorporation of palliative/supportive care end points in large clinical trials for recurrent disease should be further encouraged.

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Key issues

- Alternative therapies for recurrent ovarian cancer can be superior in terms of both clinical and quality-of-life outcomes.
- Carboplatin and pegylated liposomal doxorubicin (CD) demonstrated not only improvements in progression-free survival but also significant differences in quality of life.
- Peripheral neuropathy is both a long-lasting and bothersome side effect for ovarian cancer survivors, which may be better prevented with the use of CD compared with carboplatin and paclitaxel.
- Patients with nonmeasurable disease may still demonstrate significant abdominal discomfort and gastrointestinal symptoms, which can be helped by therapy.
- Despite improvements in some areas, fatigue and attitude/concern scores were not as significantly altered by either CD or carboplatin and paclitaxel therapy.
- CD is also preferable because of its decreased rate of alopecia and hypersensitivity, as well as its every-4-week schedule.