Title: Quality of life and treatment response among women with platinum-resistant versus platinum-sensitive ovarian cancer treated for progression: A prospective analysis.

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Abstract:

Objective. Most women with ovarian cancer relapse and undergo further chemotherapy however evidence regarding the benefits of this for women with platinum-resistant disease is limited. Our objective was to determine whether there was a quality of life improvement or treatment response among women treated for platinum-resistant recurrent ovarian cancer.

Methods. We combined data from 2 studies where women treated with chemotherapy for recurrent ovarian cancer (n=172) completed a quality of life questionnaire every 3 months. Cancers were classified as platinum-resistant if they progressed within 6 months of completing first-line chemotherapy. Mixed effects models were used to analyse change in quality of life during the first 6 months after second-line chemotherapy.

Results. One-quarter of women (n=44) were classified as having platinum-resistant disease. Overall, their quality of life did not significantly increase or decrease, following commencement of second-line chemotherapy (least square mean scores = 107, 105, 103 at chemotherapy start, 3 and 6 months later, respectively), although 26% of these women reported a meaningful increase and 31% reported a meaningful decline. One-third of the platinum-resistant group responded (11% complete and 21% partial response) to second-line chemotherapy, and this figure increased to 54% among the subset (36%) re-treated with platinum-based agents with or without other agents. Preliminary analyses suggest quality of life may be higher at chemotherapy initiation in women whose disease responded (median score 121 vs 110).

Conclusions. Overall, quality of life appears to be maintained in women with platinum-resistant ovarian cancer who receive further chemotherapy and some women respond to re-treatment.

Keywords: ovarian cancer, oncology, progression, recurrence, chemotherapy, platinum-resistance, quality of life
Introduction

Ovarian cancer is the fifth most common cause of cancer death in women [1]. Two-thirds of women diagnosed with ovarian cancer present with advanced disease and, although most initially respond to treatment, the vast majority eventually experience disease progression [2]. With few exceptions, recurrent ovarian cancer is not curable, yet end-points of most clinical trials in this group include response to treatment, progression-free survival and overall survival. In such a palliative setting, quality of life may be a more meaningful end-point.

After first-line chemotherapy for ovarian cancer, time to progression can be used to predict how groups of patients might respond to further chemotherapy at relapse [3]. A cancer with a long progression-free interval after completion of chemotherapy (>6 months) is associated with higher response rates to re-treatment, and is classified as ‘platinum-sensitive’. Management of recurrent disease in this group generally involves further platinum-based chemotherapy with response rates ranging from 30-60% and a median progression-free survival of 6-12 months [4, 5].

Women whose disease progresses within 6 months of completing first-line chemotherapy are defined as having ‘platinum-resistant’ disease. They have a 10-25% likelihood of responding to second-line chemotherapy, a median progression-free survival of 3.5-4 months and a median overall survival of 9-10 months [4, 6]. ‘Platinum-refractory’ disease refers to disease that progresses during chemotherapy and the objective response rate to second-line chemotherapy in these patients is <10% [4]. While a subset of women in these groups derive a survival benefit from second-line chemotherapy, some women with platinum-
resistant/refractory ovarian cancer continue to receive aggressive and expensive chemotherapy until days before their death [7]. The goal of end of life care is to maximize quality of life yet to date only 1 small study (n=9 with complete data) with a highly selected patient group of women with good performance status, has considered quality of life specifically among women with platinum-resistant recurrent ovarian cancer [8]. Other studies which have combined women with platinum-sensitive and resistant disease, found quality of life improvements after chemotherapy [9], however these pooled results are likely to be driven by the high proportion of women with platinum-sensitive disease. We have used 2 population-based longitudinal datasets to determine if there is a quality of life improvement following second-line chemotherapy among women with platinum-resistant ovarian cancer and have compared this group to women with platinum-sensitive disease. We also consider treatment response among these subgroups.

Methods

Study designs

We combined data from 2 longitudinal studies of women with ovarian cancer (Figure 1). Ethics approval was obtained from the Human Research Ethics Committees of the QIMR Berghofer Medical Research Institute, The University of Sydney and all participating hospitals. Participants from both studies provided informed consent.

The first study, PROSPECT [10], recruited 74 women with newly-diagnosed and 48 with recurrent disease from 7 hospitals in 2 Australian states between April 2003 and January 2005. Eligible patients were women aged 18 to 79 years referred for chemotherapy for
primary epithelial ovarian cancer and who were able to complete the study documents in English. Participants were mailed questionnaires every 3 months for 2 years or until they withdrew or died. At study entry participants were between 1 month and 20 years post-diagnosis (median 15 months).

The second study included 798 women who had participated in a previous population-based case-control study [11-13]. The Australian Ovarian Cancer Study (AOCS) recruited women aged 18–79 years with invasive epithelial ovarian cancer diagnosed between January 2002 and June 2006 through gynaecological oncology units and state-based cancer registries in all Australian states and territories. Women who participated in AOCS and were still alive between May 2005 and March 2007 were invited to take part in a quality of life substudy (AOCS-QoL) [14]. Women who consented were mailed questionnaires at 3-monthly intervals for up to 2 years, beginning 3 months to 5 years after diagnosis (median 26 months).

Women from the PROSPECT and AOCS-QoL studies were excluded from this analysis if they did not experience a progression of their disease during data collection (n=434), or did not complete a quality of life questionnaire within 2 months of starting chemotherapy for their first disease progression (n=304, including 2 with platinum-resistant and 7 with platinum-sensitive disease who did not have further chemotherapy) or if their disease was not classifiable as platinum-resistant or –sensitive (n=7 of whom 2 were platinum-refractory). We also removed duplicate data for 3 women who were in both studies leaving 172 women for analysis.
Data collection instruments and classification

Platinum status and treatment response: We reviewed medical records for date of diagnosis, start and completion dates of each chemotherapy course and cancer antigen (CA) -125 blood levels at each follow-up with the treating doctor. Platinum status was classified based on response to first-line treatment (CA-125 and CT scans when available) [4, 15, 16]. Women who had at least a partial response to first-line platinum-based chemotherapy and no disease progression within the first 6 months after completion of chemotherapy, were classified as platinum-sensitive and those who had no response and/or disease progression within 6 months of completing chemotherapy were classified as platinum-resistant. Response to chemotherapy after second-line treatment was determined based on CA-125 criteria alone. That is, compared to a pretreatment CA-125, a complete response was defined as normalization of CA-125 maintained for 28 days, a partial response was defined as at least a 50% reduction maintained for 28 days and no response was defined as no sustained reduction in CA-125.

Quality of Life: This was measured using the 39-item Functional Assessment of Cancer Therapy—Ovarian (FACT-O). The FACT-O is a multi-dimensional, ovarian cancer-specific instrument, assessing 4 general sub-scales (physical, social, emotional and functional well-being) plus an ovarian cancer and treatment specific subscale. Overall quality of life is derived from these 5 subscales. This instrument has undergone extensive reliability and validity testing showing that internal consistency and test-retest reliability are adequate [17].

Covariates: At baseline we collected self-reported demographic information including: date of birth, marital status and education level. We also collected clinical data from medical
records including: International Federation of Gynecology and Obstetrics (FIGO) disease stage at diagnosis and agents/regimen of each chemotherapy course.

Survival: Dates of disease progression and death were obtained from medical records. Clinical follow-up of progression and survival status continued until September 2010 for PROSPECT and July 2010 for AOCS. Survival time was calculated as the date of death, or if alive, end of clinical follow-up period, minus the date of first progression.

Statistical methods

We analyzed data collected during the first 6 months after second-line chemotherapy. After this there were fewer than 20 participants remaining per group. For the 14% of woman who were missing data at the 3 or 6 month data-points yet remained active in the study, we imputed the value as the average score of the time-points before and after the missing time-point. We documented reasons for dropout and calculated, at each time-point, the proportion of women who dropped out due to death or incapacity (i.e. not missing completely at random) by platinum status. To determine the likely effect of missingness [18] we graphed quality of life scores by patterns of dropout, stratified by platinum status. To determine predictors of missingness [18] we cross-tabulated the characteristics of those who dropped out versus those who did not.

We used descriptive statistics, stratified by platinum status, to calculate the proportion of women re-treated with different chemotherapy regimens and who had a response to chemotherapy. Cox regression survival analysis was used to obtain hazard ratios and 95% confidence intervals for post-progression survival by platinum status after adjustment for age.
A mixed effects repeated measures model with a random intercept and random slope was used to estimate the least squares mean scores of quality of life and wellbeing subscales by platinum status at baseline (0-2 months after the start of second-line chemotherapy) and 3 and 6 months later. We fitted the model using terms for platinum status, the interaction of platinum status with time, and covariates including age at progression and whether a woman was on chemotherapy at the time she completed the quality of life questionnaire. An unstructured covariance matrix for the random effects was used as it had the best fit for this dataset. Other key demographic and clinical covariates including marital status, education level, second-line chemotherapy with a platinum-based drug (yes, no) and second-line chemotherapy with liposomal doxorubicin (yes, no) were not included in the final models as they were not significantly associated with quality of life in fully adjusted analyses. Although not significant, age was retained as a standard covariate. Disease stage at diagnosis was not included as almost all participants (96%) were classified as late stage.

We repeated our analyses excluding women (a) who dropped out due to death or incapacity (n=31) and (b) with baseline data only (n=44), to assess the robustness of the results when different data distributions were included. Furthermore, as all models have assumptions about missing data we also conducted sensitivity analyses by fitting a repeated measures ANOVA model with last observation carried forward and a weighted generalized estimating equations model to see if the estimates were different from the mixed effects model. The results across all models were similar and thus the estimates were deemed robust (data not shown).
Clinically important changes and group differences (±) in outcomes were defined a priori as follows: 8 for the overall FACT-O scale, 2 for the FACT-O wellbeing subscales and 2.5 for cancer-specific concerns. These minimal differences were part way between the conservative half standard deviation guideline [19] and what others have reported as clinically meaningful differences in the gynecological cancer setting [20]. P-value were considered at the conventional p<0.05 level.

Results

Participants

On average, women in our analysis were 60 years of age at diagnosis (SD = 10), most (71%) were married or living with their partner, approximately three-quarters (74%) were classified as platinum-sensitive and almost all had late stage disease at diagnosis (96%) (Table 1).

Characterizing missingness

Forty percent of women dropped out of the study due to death, incapacity, unknown reason or because they had completed their commitment to the parent study (Figure 1). The proportion of dropouts due to death or incapacity was lower in the platinum-sensitive group (33%) than in the platinum-resistant group (75%). Irrespective of platinum status, women who dropped out for any reason had lower mean quality of life at baseline than those with complete data (Figure 2). Those who dropped out at the 6-month follow-up had similar absolute changes in quality of life prior to that time-point to the women with complete data (Figure 2).
There were no systematic differences in the characteristics of the 37 women who dropped out due to study completion or for unknown reasons and the 104 women with complete data (Table 1). However the 31 women who dropped out due to death or incapacity were less likely to be platinum-sensitive, less likely to have a partner, had lower baseline quality of life and had shorter survival time compared to those with complete data (Table 1).

Second-line chemotherapy agents, responses and survival by platinum-status

Most women (87%, n=111) with platinum-sensitive disease were re-treated with a platinum-based regimen (Figure 3). Approximately one-third (36%, n=16) of women with platinum-resistant disease were re-treated with platinum with or without other chemotherapy agents, while just under half (43%, n=19) were re-treated with liposomal doxorubicin (Figure 3).

Most women (84%, n=86/102 with adequate CA-125 data for evaluation) with platinum-sensitive disease had a CA-125 response to second line chemotherapy (complete response 65%, n=66; partial response 19%, n=20) compared to only 32% (n=12/38) of women with platinum-resistant disease (complete response 11%, n=4; partial response 21%, n=8). Of the women re-treated with platinum-based agents, 88% (n=79/90) of those who were platinum-sensitive and 54% (n=7/13) of those who were platinum-resistant, had a complete or partial response. Many of these women also had other agents combined with platinum that they had not received before. Five of the 7 women with platinum-resistant disease who had a response were re-treated with platinum plus paclitaxel, docetaxel, gemcitabine or liposomal doxorubicin.
Overall a total of 119 of the 172 women died during the clinical follow-up period; comprising 83 of the 128 women with platinum-sensitive disease and 36 of the 44 women with platinum-resistant disease. Women who had platinum-resistant disease had significantly worse post-progression survival than women who had platinum-sensitive disease (multivariate HR 2.34, 95% CI 1.57-3.49, p<0.001; median post-progression survival 13 versus 30 months). Among women with platinum-resistant disease, median post-progression survival was 21 months for the 16 women re-treated with platinum (and 31 months among the 7 women who responded to re-treatment) versus 10 months for the 28 women not re-treated with platinum.

Quality of life changes during and after second-line chemotherapy

Among women with follow-up data and platinum-sensitive disease, 51% (n=49) had an increase, 40% (n=39) had no meaningful change and 9% (n=9) experienced a decrease in quality of life over the 6 months after starting second-line chemotherapy. In contrast, among women with follow-up and platinum-resistant disease, 26% (n=8) had an increase, 42% (n=13) had no meaningful change and 31% (n=10) reported a decrease in quality of life.

Group differences in quality of life at chemotherapy initiation

An unadjusted comparison among women with platinum-resistant disease and follow-up data indicated that quality of life at chemotherapy initiation was no different in the 10 women who experienced a decline in quality of life compared to the 21 who had preserved or improved quality of life (median score 114 vs 112). However, among women with platinum-resistant disease median quality of life at chemotherapy initiation was higher (median score 121 vs 110) in women whose disease responded to treatment (n=12) compared to women whose
disease progressed (n=26).

Platinum status as a predictor of quality of life during and after second-line chemotherapy

Mixed effects models revealed a clinically meaningful and statistically significant group improvement in quality of life over the 6 months after starting second-line chemotherapy among women with platinum-sensitive disease, whereas there was no significant or precipitate decline among those with platinum-resistant disease (figure 4a). These results were replicated in sensitivity analyses (figure 4b & 4c). The changes in quality of life over time were statistically significantly different between the 2 groups in all models (p<0.05). Current receipt of chemotherapy was the only other factor that was significantly associated with (decreased) quality of life (p=0.008). Marital status, education level, platinum-based and liposomal doxorubicin second-line chemotherapy agents were not significantly associated with quality of life.

Within the quality of life subscales, a clinically significant but not statistically significant reduction in physical wellbeing was reported over time in women with platinum-resistant cancer, whereas a clinically and statistically significant increase in physical and functional wellbeing and an improvement in ovarian cancer-specific symptoms was reported in women with platinum-sensitive disease (Figure 5).

Discussion

This is the first population-based study to evaluate quality of life separately in women classified as having platinum-sensitive and platinum-resistant disease. We have shown that,
overall, among women classified as having platinum-resistant disease, retreatment with chemotherapy when they experience a recurrence does not significantly improve or diminish their quality of life. However, one-quarter and one-third of this group respectively report meaningful increases and decreases in quality of life. Like others [5, 6] we confirmed that for women with platinum-resistant ovarian cancer, complete tumor response is rare and survival is significantly poorer than for women with platinum-sensitive disease. Importantly though, a subset of women with apparently platinum-resistant tumors do respond to re-treatment.

Notably, as reported here and elsewhere [21], the response in women with platinum-resistant disease appears to be better for those re-treated with platinum-based agents ± other agents than the response in those re-treated with liposomal doxorubicin or taxane alone. Larger studies adjusting for characteristics of women selected to receive platinum are needed to confirm this result and to determine if there is also a quality of life improvement or maintenance.

In women with platinum-resistant disease maintenance of quality of life may be a useful outcome, as there is a possibility that without chemotherapy quality of life would have rapidly declined due to disease progression. This conclusion however is to be taken with caution. We were unable to compare the quality of life trajectory of women not given second-line chemotherapy following disease progression since almost all women went on to receive second-line chemotherapy. We also show that aside from platinum-status the only other factor that was associated with improved quality of life within our overall sample was cessation of chemotherapy. Furthermore, our analyses may underestimate decline in quality of life among women with platinum-resistant disease as computation of missingness in the mixed effects model is based on the observed data distribution and those women who dropped out of the study due to incapacity were likely to have poorer quality of life.
Our results highlight the need for detailed investigation into which women with platinum-resistant ovarian cancer will and will not benefit from chemotherapy in the later stages of their disease course. Our preliminary subgroup analysis gives an indication that quality of life at the start of chemotherapy may be correlated with having a response to treatment. If this were to be confirmed with a larger sample it is possible that quality of life screening at the start of treatment may be a useful clinical practice in this particular group of patients. This is important preliminary information since the decision to re-treat women with platinum-resistant disease may come at considerable cost, both in terms of increased patient morbidity, and to the health system in terms of expenditure which is estimated at USD $20,744 on average per woman after first-line chemotherapy [22].

In conclusion, this study raises important ethical and economic questions about the re-treatment of women with platinum-resistant ovarian cancer with chemotherapy. Disease response rates are particularly low in those not treated with platinum and approximately one third of women in the platinum-resistant group when treated with second-line chemotherapy have significant declines in quality of life. Further research in a larger series of patients with platinum-resistant disease should be conducted to identify the groups most likely to benefit from re-treatment with chemotherapy. Given that the majority of women with ovarian cancer will have a progression and that approximately one-quarter will be classified as having platinum-resistant disease, evaluation of both the costs and benefits of treating this disease is essential for efficient use of limited health care resources and optimal patient-centered care [23].
Acknowledgments

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Conflicts of interests

A. deFazio holds a patent unrelated to this manuscript and has received a Speaker's Honorarium from Roche. All remaining authors have declared no conflicts of interest.
References


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Figure 4b. Least squares mean quality of life scores following second-line chemotherapy in women with ovarian cancer treated for platinum-sensitive (n=112) versus -resistant (n=29) disease. Sensitivity model: not including women who dropped out due to death or incapacity.

Figure 4c. Least squares mean quality of life scores following second-line chemotherapy in women with ovarian cancer treated for platinum-sensitive (n=97) versus -resistant (n=31) disease. Sensitivity model: not including women with baseline only data.

Figure 5. Wellbeing subscale breakdown of overall quality of life presented in figure 4a.
Table 1: Demographic and clinical characteristics of all participants and by missingness type

<table>
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<tr>
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<th>All participants (n=172)</th>
<th>Participants with complete data (n=104)</th>
<th>Dropout due to death or incapacity (n=31)</th>
<th>Dropout due to completed study or unknown reason (n=37)</th>
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<td>Platinum sensitive, %</td>
<td>74</td>
<td>77</td>
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<td>Age at progression, mean (SD)</td>
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<td>74</td>
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<td>Stage III or IV at diagnosis, %</td>
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<td>97</td>
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<td>QoL at second-line chemotherapy initiation, mean (SD)</td>
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<td>108 (22)</td>
<td>96 (22)*</td>
<td>105 (21)</td>
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<td>Survival from second-line chemotherapy initiation (months), median</td>
<td>26</td>
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* Different from all participants
Figure 1. Flow of participant recruitment and data contribution to this analysis

<table>
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<td></td>
<td>44</td>
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<tr>
<td>AOCS-QOL study</td>
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<td>March 2007</td>
<td>798</td>
</tr>
<tr>
<td>Completed questionnaire</td>
<td>May 2005</td>
<td>March 2007</td>
<td>130</td>
</tr>
</tbody>
</table>

- 3 month follow-up data = 128 (74%)
  - PS withdrawals: death = 7, incapacity = 4, completed follow-up = 7, unknown = 13.

- 6 month follow-up data = 104 (60%)
  - PS withdrawals: death = 2, incapacity = 3, completed follow-up = 4, unknown = 8.
  - PR withdrawals: death = 4, incapacity = 2, unknown = 1.

*Completed follow-up for parent study
Figure 2. Mean quality of life score by dropout time stratified by platinum status.
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Note: All models adjusted for age at progression and whether currently on chemotherapy. Marital status, education, second-line chemotherapy with platinum or liposomal doxorubicin were tested and not included as covariates due to their lack of association.

Note: A difference of 8 on the FACT-O scale is considered clinically significant.
Figure 5. Wellbeing subscale breakdown of overall quality of life presented in figure 4a.

Note: A difference of 2 on the wellbeing scales and 2.5 on the ovarian cancer-specific concerns scale is considered to be a clinically significant least squares mean difference. Statistical support (p<0.05) for changes were noted in physical, functional, emotional wellbeing and ovarian cancer-specific concerns among women who had platinum-sensitive disease.