compared with bone metastasis. But as the overall survival from timepoint of diagnosis of the metastasis was quite similar in both studies with 7.2 and 7.4 months, this argument alone is not sufficient to explain the differences found in both analyses.

Conclusion
The most important finding of this study was the different prognostic impact of early-onset bone metastasation in comparison to late-onset bone manifestation. The fact that late-onset bone spread hardly influences the overall prognosis should be remembered by the clinician, before limiting the patient to a purely symptomatic therapy regime due to the finding of bone metastases only.

disclosure
The authors have declared no conflicts of interest.

references

Platinum versus platinum-combination chemotherapy in platinum-sensitive recurrent ovarian cancer: a meta-analysis using individual patient data

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Received 22 April 2013; revised 1 August 2013; accepted 21 August 2013

Background: The majority of women with ovarian cancer develop recurrent disease. For patients with a platinum-free interval of >6 months, platinum-based chemotherapy is a treatment of choice. The benefit of platinum-based combination chemotherapy in randomized trials varies, and a meta-analysis was carried out to gain more secure information on the size of the benefit of this treatment.

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Materials and methods: We initiated a systematic review and meta-analysis following a pre-specified protocol to determine whether combination chemotherapy is superior to single-agent platinum chemotherapy in women with relapsed platinum-sensitive ovarian cancer.

Results: A total of five potentially eligible randomized trials were identified that had used combination-platinum chemotherapy versus single-agent platinum chemotherapy in women with relapsed platinum-sensitive ovarian cancer. For one trial (190 patients), adequate contact with the investigators could not be established. Therefore, four trials that randomly assigned 1300 patients were included, with a median follow-up of 36.1 months. Overall survival (OS) analyses were based on 865 deaths and demonstrated evidence for the benefit of combination-platinum chemotherapy (HR = 0.80; 95% CI, 0.64–1.00; P = 0.05). Progression-free survival (PFS) analyses were based on 1167 events and demonstrated strong evidence for the benefit of combination-platinum chemotherapy (HR = 0.68; 95% CI, 0.57–0.81; P < 0.001). There was no evidence of a difference in the relative effect of combination-platinum chemotherapy on either OS or PFS in patient subgroups defined by previous paclitaxel (Taxol) treatment (OS, P = 0.49; PFS, P = 0.66), duration of treatment-free interval (OS, P = 0.86; PFS, P = 0.48) or the number of previous lines of chemotherapy (OS, P = 0.21; PFS, P = 0.27).

Conclusions: In this individual patient data (IPD) meta-analysis, we have demonstrated that combination-platinum chemotherapy improves OS and PFS across all subgroups. This provides the strongest evidence to date of the benefit of combination-platinum over single-agent platinum.

Key words: IPD meta-analysis, recurrent ovarian cancer

introduction

Ovarian cancer is the seventh most common cancer in women worldwide. Globally, there are an estimated 225,000 new cases and 140,000 ovarian cancer-related deaths annually (Globocan). The majority of women present with advanced disease (70%–85%). Optimal management with maximal surgical debulking and platinum-based chemotherapy induces remission in a significant proportion. However, this is usually temporary and the majority of women will subsequently relapse (60%–65%) and be offered further chemotherapy treatment.

Platinum-based drugs remain as the most active agents in ovarian cancer with carboplatin and cisplatin having a similar efficacy [1, 2], but carboplatin having a more favourable toxicity profile. Decisions about the most appropriate treatment at relapse are primarily dependent on the duration of response to the previous platinum-based chemotherapy. When the treatment-free interval is >6 months, patients are considered to have platinum-sensitive disease and are likely to respond to further platinum treatment. Those patients relapsing during initial treatment or within 6 months of completing treatment are classified as platinum-resistant and are unlikely to respond to further platinum-based regimens; therefore, other second-line agents are usually considered [3–5]. These definitions are >20 years old but nevertheless remain clinically relevant and are routinely used to define eligibility in relapsed ovarian cancer trials and to facilitate decision-making in the clinic.

The majority of patients have platinum-sensitive disease and a number of drugs, alone and in combination, have demonstrated significant activity in this group of patients. Several randomized, controlled trials (RCTs) have compared single-agent carboplatin with a platinum-combination in platinum-sensitive recurrent ovarian cancer [6–10]. Carboplatin monotherapy is highly convenient to administer, well-tolerated and produces relatively high response rates. In many respects, carboplatin fulfills the major requirements for treatment of patients with incurable ovarian cancer. However, platinum-combination regimens have demonstrated greater activity than single-agent carboplatin in randomized and non-randomized trials. Platinum combinations inevitably lead to greater toxicity and only one RCT has demonstrated a significant improvement in overall survival (OS) [6]. Other studies have shown significant prolongation of progression-free survival (PFS) [7] or little benefit of platinum-combination therapy compared with single-agent carboplatin [10]. It is important to know the real value of platinum-combination chemotherapy. If the benefit is small or not significant it may be better to use a single-drug sequentially.

We also made comparisons to investigate the benefit or lack of benefit of platinum-combination chemotherapy versus platinum alone in three pre-specified subgroups: those who had paclitaxel chemotherapy as part of first-line treatment compared with those who did not, patients with a treatment-free interval of >12 months compared with those of 6–12 months and patients who had received one prior line of chemotherapy compared with those who received more than one line.

To the best of our knowledge, this is the only individual patient data (IPD) meta-analysis in platinum-sensitive recurrent ovarian cancer of platinum monotherapy versus platinum-combination chemotherapy. We believe that it provides the most robust evidence for the use of platinum-chemotherapy in recurrent platinum-sensitive recurrent ovarian cancer.

methods

The aim was to determine whether platinum-combination chemotherapy is superior to single-agent platinum chemotherapy in women with relapsed platinum-sensitive ovarian cancer. The systematic review and meta-analysis followed a detailed and pre-specified protocol which stated the objectives, trial inclusion and exclusion criteria, search methods, data to be collected and statistical analyses to be carried out. A copy of the protocol is available from the authors upon request. The quality of the RCTs was checked using standardized checks listed below and reviewing the trial protocols and published papers.

inclusion and exclusion criteria

Trial inclusion criteria: phase II and III RCTs; trials closed to patient accrual; trials comparing single-agent platinum chemotherapy with platinum-based combinations in platinum-sensitive relapsed epithelial ovarian cancer.
search methods

Trials were identified by using electronic databases. MEDLINE and EMBASE were searched using an optimal search strategy [11] and regular systematic searches were carried out to identify as many relevant trials as possible. In addition, a number of trial sources were utilized to ensure a comprehensive and up-to-date database of trials, including Physician Data Query, National Cancer Institute Clinical Trials, UK Coordination Committee on Cancer Research (UKCCCR) register of cancer trials. Hand searches of meeting proceedings were also carried out to ensure trials only presented in abstract form and were not missed: American Society of Clinical Oncology ASCO (1990–2012), International Gynecologic Cancer Society (1991–2012) and Society of Gynecologic Oncology (1990–2012). Experts in the field were consulted to confirm if there were any unpublished/ negative trials that were not identified using the above search strategies.

data collection and checking

For each eligible trial identified, the following baseline and outcome data were collected from the principal investigator, where possible. Baseline characteristics are unique patient identifier, date of birth/age, histology, performance status, number of previous lines of chemotherapy, previous paclitaxel treatment, duration of treatment-free interval, date of randomization and allocated treatment. Outcomes are progression status, date of progression, survival status, date of death/last follow-up, cause of death, whether excluded from analysis and reason for exclusion.

A number of standard checks were applied to all trials, including checks for missing values and data validity and consistency across variables. To assess the randomization integrity, we looked for unusual patterns in the sequencing of allocation or imbalances in the number of patients who are randomized to each treatment arm. Follow-up of surviving patients was also assessed to ensure that it was balanced by treatment arm and as up-to-date as possible. Any queries were resolved and the final database entries verified by the responsible trial investigator and statistician.

statistical analysis

Analyses of outcomes, trial groups and patient subgroups were pre-specified in the protocol and carried out on an intention-to-treat basis. Analyses of all end points were stratified by trial, and the log-rank expected number of deaths and variance was used to calculate individual trial hazard ratios (HRs) and overall pooled HRs based on the random-effect model [12]. Thus, the times to death for individual patients were used within trials to calculate the HR, representing the overall risk of an event for those patients allocated to single-agent platinum chemotherapy compared with those allocated to platinum-combination chemotherapy.

The primary end point was OS, measured from the date of random assignment until death by any cause, patients remaining alive and those lost to follow-up were censored on the date of last follow-up. The secondary end point was PFS, measured from the date of random assignment until progression of disease, recurrence or death from any cause. The median

<table>
<thead>
<tr>
<th>Trial</th>
<th>ICON &amp; AGO</th>
<th>ICON</th>
<th>AGO</th>
<th>ACO</th>
<th>P \textsuperscript{a}</th>
<th>MRC CTU</th>
<th>FIGO, International Federation of Gynecology and Obstetrics, MRC CTU: Medical Research Council Clinical Trials Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Europe \textsuperscript{a}</td>
<td>Europe \textsuperscript{b}</td>
<td>USA</td>
<td>Spain</td>
<td>Italy</td>
<td>Italy</td>
<td>Italy</td>
</tr>
<tr>
<td>Patients randomized</td>
<td>356</td>
<td>882</td>
<td>81</td>
<td>81</td>
<td>137</td>
<td>593</td>
<td>593</td>
</tr>
<tr>
<td>FIGO stage</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Median follow-up (months)</td>
<td>42.5</td>
<td>27.1</td>
<td>59.3</td>
<td>13.7</td>
<td>Not available</td>
<td>9.5</td>
<td>10.7</td>
</tr>
<tr>
<td>Planned carboplatin dose</td>
<td>AUC 5 (75 mg/m\textsuperscript{2} in controls)</td>
<td>AUC 5</td>
<td>AUC 5</td>
<td>AUC 5</td>
<td>AUC 5</td>
<td>AUC 5</td>
<td>AUC 5</td>
</tr>
<tr>
<td>Planned combination dose</td>
<td>Paclitaxel 175 mg/m\textsuperscript{2}</td>
<td>ICON 185 mg/m\textsuperscript{2}</td>
<td>AGO</td>
<td>Gemcitabine 1000 mg/m\textsuperscript{2} d1,d8 q3 weeks. PLDb 30 mg/m\textsuperscript{2}</td>
<td>Paclitaxel 175 mg/m\textsuperscript{2}</td>
<td>Epipodophyllotoxin 120 mg/m\textsuperscript{2}</td>
<td>Paclitaxel 175 mg/m\textsuperscript{2}</td>
</tr>
<tr>
<td>Planned treatment duration</td>
<td>6 cycles every 4 weeks</td>
<td>6 cycles every 3 weeks</td>
<td>6 cycles every 3 weeks</td>
<td>6 cycles every 3 weeks</td>
<td>6 cycles every 3 weeks</td>
<td>6 cycles every 3 weeks</td>
<td>6 cycles every 3 weeks</td>
</tr>
</tbody>
</table>

\textsuperscript{a}UK, Norway and Switzerland; Germany; Italy. Pegylated liposomal doxorubicin.
follow-up was calculated by the reverse Kaplan–Meier method, based on surviving patients and using censoring as the event.

The relative effects of platinum-combination chemotherapy in different subgroups of patients were investigated. Analyses were carried out for each pre-specified subgroup: comparing the effect of combination and single-agent platinum by previous paclitaxel chemotherapy, treatment-free interval and number of previous lines of chemotherapy within each individual trial. \( \chi^2 \) tests for interaction were used to investigate whether there were any substantial differences in the effect of platinum-combination chemotherapy between subgroups of patients. \( \chi^2 \) heterogeneity tests and the \( I^2 \) statistic for inconsistency were used to assess statistical heterogeneity across trials [13]. The data analysis for this paper was generated using SAS software version 9.3 (SAS Institute, Cary NC), and included in the meta-analysis using RevMan 5.1 software (Cochrane Collaboration, Copenhagen, Denmark). All \( P \) values quoted are two-sided.

results

A total of five potentially eligible trials that had used platinum-combination chemotherapy versus single-agent platinum chemotherapy in women with relapsed platinum-sensitive ovarian cancer were identified. For one trial (190 patients), adequate contact with the investigators could not be established. Therefore, four trials that randomly assigned 1300 patients were included. These represent 87% of patients from all known randomized trials that compared platinum-combination chemotherapy with single-agent platinum chemotherapy in women with relapsed platinum-sensitive ovarian cancer. The four trials accrued between 61 and 802 patients; characteristics of these trials are summarized in Table 1. The median follow-up for all surviving patients was 36.1 months (IQR: 22.7–55.9 months).

Table 2. Patient subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Response</th>
<th>Single (( n = 658 ))</th>
<th>Combination (( n = 642 ))</th>
<th>Total (( n = 1300 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous paclitaxel:</td>
<td>Yes</td>
<td>356 (54.1)</td>
<td>349 (54.4)</td>
<td>705 (54.2)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>302 (45.9)</td>
<td>293 (45.6)</td>
<td>595 (45.8)</td>
</tr>
<tr>
<td>Duration treatment-free interval:</td>
<td>6–12</td>
<td>200 (30.7)</td>
<td>190 (30.1)</td>
<td>390 (30.4)</td>
</tr>
<tr>
<td></td>
<td>&gt;12</td>
<td>452 (69.3)</td>
<td>442 (69.9)</td>
<td>894 (69.6)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>6</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Number of previous lines:</td>
<td>1</td>
<td>623 (94.7)</td>
<td>596 (93.1)</td>
<td>1219 (93.9)</td>
</tr>
<tr>
<td></td>
<td>&gt;1</td>
<td>35 (5.3)</td>
<td>44 (6.9)</td>
<td>79 (6.1)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

OS

OS analyses were based on 865 deaths from four trials. Figure 1A shows evidence for the benefit of platinum-combination chemotherapy (HR = 0.80; 95% CI, 0.64–1.00; \( P = 0.05 \)). There was moderate, but non-significant, heterogeneity among the trials (\( P = 0.14; I^2 = 45\% \)).

PFS

PFS analyses were based on 1167 events from four trials. Figure 1B shows strong evidence for the benefit of platinum-combination chemotherapy (HR = 0.68; 95% CI, 0.57–0.81; \( P < 0.001 \)). There was moderate, but non-significant, heterogeneity between the trials (\( P = 0.19; I^2 = 36\% \)).

patient subgroups

There was no clear evidence of a difference in the relative effect of platinum-combination chemotherapy on OS in patient subgroups defined by previous paclitaxel treatment (\( P = 0.49 \)), duration of treatment-free interval (\( P = 0.86 \)) or the number of previous lines of chemotherapy (\( P = 0.21 \)). Also, there was no clear evidence of a difference in PFS in patient subgroups defined by previous paclitaxel treatment (\( P = 0.66 \)), duration of...
treatment-free interval ($P = 0.48$) or the number of previous lines of chemotherapy ($P = 0.27$). The number of patients in each subgroup is shown in Table 2; within-subgroup estimates are presented in Figure 2.

Limiting the subgroup analysis to investigate those patients who received paclitaxel–platinum for first-line and second-line treatments gave similar results with no difference in OS ($P = 0.57$) and PFS ($P = 0.77$).
including the Bolis et al. (2001) trial [10]—‘data unavailable for analysis’

A total of 190 subjects entered the study. The 3-year OS was 29% with carboplatin alone and 42% with carboplatin plus epidoxorubicin (odds ratio = 0.8; 95% CI, 0.6–1.2). The 3-year PFS was 12% and 25%, respectively, in the carboplatin alone and carboplatin plus epidoxorubicin groups (OR = 0.6; 95% CI, 0.5–1.0).

Combining these published results with the four trials for which IPD was available had little effect on the point estimates and confidence intervals (Figure 3). The benefit of platinum-combination chemotherapy on OS is estimated at 0.81 (95% CI, 0.69–1.0).

PFS was 12% and 25%, respectively, in the carboplatin alone and carboplatin plus epidoxorubicin groups (OR = 0.6; 95% CI, 0.6–1.0).

Discussing these published results with the four trials for which IPD was available had little effect on the point estimates and confidence intervals (Figure 3). The benefit of platinum-combination chemotherapy on OS is estimated at 0.81 (95% CI, 0.69–0.96), and 0.69 (95% CI, 0.60–0.79) for PFS. There was no evidence of heterogeneity between the trials (OS: P = 0.24, I² = 27%; PFS: P = 0.29, I² = 19%).

Discussion

We found five RCTs comparing single-agent platinum with a platinum-combination in platinum-sensitive recurrent ovarian cancer [6–10]. All five trials have been published in peer-reviewed journals; however, the data from one trial [10] were not available to include in the IPD meta-analysis, thus two analyses were carried out; first, using IPD for the four trials alone and second, combining the IPD data with published results from the Bolis trial [10]. The primary objective of carrying out this meta-analysis was to produce an improvement in the power of the smaller studies to answer the question of the benefit of platinum-combination chemotherapy over platinum monotherapy in patients with platinum-sensitive recurrent ovarian cancer. In addition, there is the advantage of gaining greater statistical power to carry out subgroup analyses.

On the basis of these five trials there is evidence to support the use of platinum-combination chemotherapy for platinum-sensitive ovarian cancer, with a 20% reduction in the relative risk of death compared with single-agent platinum chemotherapy. There is also strong evidence for the benefit of platinum-combination chemotherapy on PFS, with a 30% reduction in the relative risk of progression.

The ICON4/AGO-OVAR 2.2 trial [6] is the largest trial to compare combination-platinum with single-agent carboplatin. It was a practice changing trial with carboplatin–paclitaxel becoming an internationally accepted standard of care for patients with platinum-sensitive recurrent ovarian cancer. However, a few controversies emerged from the trial results which this IPD meta-analysis can address. At the time the study was conducted, 43% of women had not received a taxane as part of their first-line treatment. Therefore, the benefit seen in recurrent ovarian cancer of combination treatment was thought by some to be an effect in the no-taxane arm. In this IPD analysis of all trials, in a subgroup analysis, we have demonstrated that there is no evidence of a difference in OS or PFS in patients who had previous paclitaxel and those who had no previous paclitaxel as part of first-line treatment.

Furthermore, there was no evidence of a difference in the relative effect of platinum-combination chemotherapy in the other subgroups: patients with a treatment-free interval of >12 months compared with those who had a treatment-free interval of only 6–12 months and patients who had received 1 prior line of chemotherapy were compared with those who had received more than one line of prior chemotherapy. However, only 6% of patients had received more than one line of prior chemotherapy. In this IPD meta-analysis we have demonstrated that combination-platinum chemotherapy improves OS and PFS across all subgroups. This provides the strongest evidence to date of the benefit of combination-platinum over single-agent platinum. Quality-of-life data were only available for two trials [7, 8] and thus was not part of the meta-analysis. These trials demonstrated no worsening in QOL between the single-agent and combination-platinum arms.

The trials in the IPD were carried out from 1991 to 2004, and since then there have been significant developments in the treatment of recurrent platinum-sensitive ovarian cancer. The CALYPSO (Caelyx in Platinum-Sensitive Ovarian Patients) trial compared two platinum combinations, carboplatin–paclitaxel and carboplatin–pegylated liposomal doxorubicin (PLD) [14]. This was designed as a non-inferiority trial, and it demonstrated that the PFS following the carboplatin–PLD regimen was statistically superior to carboplatin–paclitaxel.

Finally, many of the large number of biological agents at varying stages of development are under investigation in recurrent ovarian cancer. Many of these are being evaluated in combination with chemotherapy and then continued as maintenance treatment. Carboplatin combinations with paclitaxel or gemcitabine are being used as the ‘backbone’ of chemotherapy to evaluate these targeted molecules. For example, a phase III trial has demonstrated that the addition of the anti-angiogenic agent, bevacizumab to carboplatin and gemcitabine significantly improved the tumour response rate and PFS in patients with a first ‘platinum-sensitive’ recurrence of ovarian cancer [15]. In Europe, bevacizumab has now been licensed for treatment of this group of women when given in combination with carboplatin and gemcitabine. The combination of other targeted drugs such as the vascular endothelial growth factor receptor tyrosine kinase inhibitors [e.g., cediranib, ICON6 trial (NCT00532194)] are being investigated in combination with platinum doublets. Other targeted agents, such as PARP inhibitors [16–18] are very likely to play an important role in the treatment of recurrent ovarian cancer.

Patients are now surviving longer after their disease has recurred than before, largely due to the careful use of chemotherapy for recurrent ovarian cancer. Some patients receive up to six lines of chemotherapy for their relapsed disease [19, 20]. The judicious use of chemotherapy at relapse is therefore of paramount importance. We have demonstrated that the use of combination-platinum chemotherapy improves OS and PFS across all subgroups in recurrent ovarian cancer, thus, providing the strongest evidence to date that combination therapy should be considered as the standard of care for those women who are fit to receive combination therapy.

Funding

FAR and NC are supported by Cancer Research UK. Grant C444/A4125.
disclosure

The authors have declared no conflicts of interest.

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