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Editorial

Progression-free *versus* overall survival and adequate powering in randomised studies

Randomised data from over a decade ago have been used to adopt the combination of a platinum agent with a taxane as the standard of care in the first line therapy of advanced epithelial ovarian cancer.[1] Whilst this two-drug regimen is effective, recurrence is common and thus, a number of trials have attempted to identify a suitable candidate for incorporation as a third non-cross-resistant drug. The anthracyclines have long been considered as a candidate for this 'third drug' and early meta-analyses[2–4] suggested that the addition of doxorubicin to standard regimens conferred a survival benefit to a similar magnitude to that of platinum, though some observed that triplet combinations had a higher incidence of toxicity.

In this issue of the *European Journal of Cancer*, Aravantinos *et al*. report the results of a randomised study to compare the effects on overall survival (OS) and progression-free survival (PFS) of carboplatin dosed with an AUC of 7 and paclitaxel, with cisplatin at 75 mg/m^2, paclitaxel and doxorubicin with G-CSF support in the treatment of advanced ovarian epithelial cancer. A total of 451 patients were stratified according to the stage of their cancer (IIc *versus* III *versus* IV) and the presence of residual disease. Response rates were similar, and there were no significant differences in median PFS (13.25 *versus* 18.13 months $p = 0.07$) or OS with addition of the anthracycline. In fact, though the 3-year and 5-year OS rates were non-significantly lower in the control group, the 1 year OS rate was actually 3% lower for the triplet group (84% *versus* 87.4%), though once again this was not significant further emphasising the lack of a clinically meaningful survival improvement. There was also no difference between the two groups in terms of time to treatment failure. Chemotherapy was found to be generally well tolerated, though the incidence of febrile neutropaenia was higher in the anthracycline arm (4% *versus* 12%, $p = 0.006$).

The importance of proving clinical benefit in oncology drug trials is demonstrated in the US Food and Drug Administration's (FDA) current requirement for evidence of prolongation of survival or symptom improvement for drug approval, whereas previously this could be given on the basis of tumour response rate alone. This applies throughout disease, be it first line treatment or in the setting of platinum resistance. OS is defined as the time from randomisation until death from any cause, and is understandably considered the gold-standard though subsequent second and third line therapies including cross-over can confound analyses. PFS (the time from randomisation to the date progression of the disease was firstly documented) can also be considered as a primary end-point, but assigning a date for progression measurement can introduce bias as these measures are sensitive to the timing of the investigation. With the measurement of survival the exact date of death is known, whereas the exact date of progression can be difficult to determine unless assessments are made very frequently. Measurement of PFS in open-label studies such as this are thought to be especially susceptible to assessment bias, and thus blinding would usually be preferred.[5] No information was given in the study as to which criteria were used to measure progression and if these and the exact timing of assessment were symmetrical between study arms.

The FDA has conducted simulation studies in the past to illustrate that in a large open-labelled study, a very subtle systematic study arm bias may produce false positive statistically significant differences in median PFS. The simulation results suggested that there was a very high probability of falsely inferring treatment differences in PFS even if the assessment schedules between the study groups differ only by 2 d, and this increases rapidly as sample sizes increase.[6] In addition to the effect of evaluation-time bias on PFS, it is worth considering the role of bias caused by more patients withdrawing from the investigational arm than the control arm without documented progression. With the use of OS as the end-point these patients could still be followed for death, whilst the documentation of progression would be near impossible. In this study, exactly double the number of individuals discontinued intervention in the experimental arm (46 *versus* 23 patients), which could have lead to a degree of attrition bias effecting the final difference in PFS between the groups. However, given that both these numbers were small in relation to the overall number of patients in each group, the effect may not have been substantial. Furthermore, as Aravantinos et al., note, the small difference in terms of performance status in the treatment group could also have influenced the final PFS outcome.

Despite the lack of translation of Aravantinos et al.'s results to a clear survival benefit for ovarian cancer patients, the study has several strengths. They adhered to the GCIG

OCCC 2004 recommendation that phase III studies looking at first line treatment for advanced ovarian cancer should be powered so that both PFS and OS can be appropriately measured, with either designated as the primary end-point.[7] Negative data such as these merit publication and we are mercifully free of multiple *post hoc* sub-group analyses to salvage underpowered end-points or those that fail to reject the null hypothesis (such *post hoc* dredging is akin to firing a bullet and being allowed to draw the target afterwards, or using multiple targets in the case of multiple bullets, regardless of the 'pre-specified' nature of such targets). The involvement of a large number of patients in this study should also be acknowledged especially from one of the smaller European countries, as does the finding that the anthracycline treatment was generally well tolerated (albeit with G-CSF support), as previous studies had reported high incidences of toxicity with their use.

The authors' finding of a marginal increase in PFS should not be completely discredited either. For example, in 2006 the FDA took the rare step of approving the drug gemcitabine for the treatment of recurrent ovarian cancer, by overruling its own advisory panels 9-2 vote against such approval.[8] The study referred to involved 356 patients, and found a significant 2.8-month increase in median PFS when the combination of gemcitabine and carboplatin was used compared with carboplatin alone, but there was no reported difference in patients' OS. The panel but not the FDA itself was of the view that the differences in the way progression was evaluated, with objective, clinical and radiological measures, resulted in the outcome reflecting investigator bias. Despite the advisory panel's reservations over the nature of the results, the FDA approved gemcitabine. This was considered to be the first time when approval was given for an ovarian cancer drug based upon PFS rather than an improvement in OS. In support of the use of PFS to evaluate the efficacy of a drug, it could be argued that progression is inevitably followed by morbidity and mortality, thus delaying the progression of cancer may be of direct benefit to patients. Prolonging PFS can delay the onset of symptoms and avoid the psychological burden associated with disease progression and changing therapy. Furthermore, it is insensitive to subsequent therapy outside of the current study and a higher proportion of events are thought to be informative than with OS, as deaths included may be unrelated to the disease process.

Even though early results were encouraging, more recent randomised clinical trials have also found that OS or PFS were not improved by the addition of an anthracycline to the standard regimen.[9,10] In 1995 A'Hern and Gore overviewed a number of studies and compiled data from 1702 patients to demonstrate that the addition of doxorubicin did confer a significant survival benefit[2]. They raised the question that it is difficult to determine whether the improved survival is a result of increased dose-intensity, as opposed to solely due to doxorubicin addition. Furthermore, the studies they used did not include a taxane in the regimen and 5 of the 11 included did not contain platinum, suggesting that perhaps examining the effect of anthracycline replacement in the current two-drug regimen, rather than its addition, could be more useful.

The concept of incorporating new drugs in first-line regimens in ovarian cancer cannot be considered a failure, and there may also be a role for investigating patient-reported outcomes such as quality of life or symptom assessment as part of the interpretation of treatment implications. Nevertheless, in spite of the efforts thus far, improving the standard platinum/paclitaxel combination for advanced ovarian cancer is not proving an easy task.

Conflict of interest statement

None declared.

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