Does clinical trial participation improve outcomes in patients with ovarian cancer?

L Khoja,1 L Horsley,1 A Heesters,2 J D Machin,1 C Mitchell,1 AR Clamp,1 GC Jayson,1 J Hasan1

ABSTRACT

Introduction: Treatment on a clinical trial is considered to be beneficial to oncology patients. However, supportive evidence for this is scarce. Trial effect describes the phenomenon of improved health outcomes in patients treated with standard of care (SOC) on trial compared to those receiving SOC outside of a clinical trial. We evaluated trial effect in patients with ovarian cancer treated at our tertiary cancer centre.

Methods: We performed a retrospective cohort study of patients with ovarian cancer treated at The Christie National Health Service Foundation Trust. Patients treated on one of three first-line clinical trials: (SCOTROC-4, ICON-5, ICON-7) were matched (for age, International Federation of Gynaecology and Obstetrics stage, surgical status and performance status) with individuals receiving the same SOC off trial. Survival was calculated using Kaplan-Meier methodology.

Results: 60 patients were evaluated; 30 on trial and 30 on SOC off trial. The median progression-free survival (PFS) was 21.8 months (control group) and 25.9 months (trial group), median overall survival (OS) was 64.3 months (control group) and 68.9 months (trial group). There was no difference in PFS (log-rank test: HR 0.87 (95% CI 0.48 to 1.54), p=0.6) or OS (log-rank test: HR 0.87 (95% CI 0.46 to 1.64), p=0.7) between groups.

Conclusions: Patient survival was similar regardless if treated on trial or as SOC. Our findings do not support trial effect, at least in a tertiary cancer centre. Clinical trial participation in specialised cancer centres promotes best practice to the benefit of all patients. These findings may impact discussions round consent and organisation of oncology services.

INTRODUCTION

Participation in clinical trials is often promoted as the best treatment option for patients with cancer. While some clinical trials have the potential to offer more effective treatments than standard of care (SOC)—BRAF inhibitors and checkpoint inhibitor antibodies in metastatic melanoma being prominent examples1–4—most randomised clinical trials (RCTs) do not produce positive outcomes. In a systematic review of 255 RCTs, two-thirds of clinical trials failed to meet their primary endpoints.5 Furthermore, in large phase III trials where SOC is used as a control arm, up to half of enrolled patients will not experience any additional therapeutic benefit. It is important to ask, therefore, whether receiving SOC on trial results in improved outcomes for these patients.

‘Trial effect’ describes the phenomenon of improved health outcomes in patients treated with SOC on trial compared to those receiving SOC outside of a clinical trial.
setting. A number of variables have been posited as contributors to this so-called effect but it is unclear whether these are attributable to the treatment setting (which tends to be tertiary centres with greater expertise and resources than hospitals that are not research-intensive) or explainable by other psychologically-mediated factors such as patients’ or clinicians’ increased expectations of success. The trial effect may, moreover, simply be an illusion created by selection bias, as stringent eligibility criteria that exclude less fit patients may mean trial participants are already likely to fare better than their counterparts receiving SOC outside of the research context.

If health outcomes are superior in patients receiving SOC on trial, then the push to enrol patients into trials may be justified even if some patients will be disappointed when they are deemed ineligible to participate. From an ethical perspective, a better understanding of trial effect is essential because it challenges a concern of those involved in the research ethics review process. Since Appelbaum et al first introduced the concept of the therapeutic misconception in 1982, clinician-researchers have been urged to avoid descriptions of their trials that may confute research and therapeutic aims; however, despite decades of work on the language of informed consent, the distinction is quickly blurred when participants are desperate for cures and researchers are eager to confer benefits on them.

There is a paucity of evidence in the literature on ‘trial effect’. Published systematic reviews have not supported its existence, but these were largely conducted before many SOC regimens were adopted and were further hampered by lack of adequately matched controls to allow reliable comparisons between patient groups. We sought to evaluate the existence of ‘trial effect’, by conducting a retrospective cohort study comparing patients with ovarian carcinomas treated with SOC on trial with patients treated with the same SOC but off trial.

**METHODS**

This retrospective cohort study included patients with epithelial ovarian cancer treated at The Christie NHS Foundation Trust, a tertiary oncology referral centre. Patients with epithelial ovarian cancer treated on three large UK first-line clinical trials: SCOTROC-4, ICON-5, ICON-7, from 2002 to 2008, were each matched with individuals who received the same chemotherapy outside of a clinical trial. Cases were matched with controls on a 1:1 ratio for the following: age (<65 years or >65 years), International Federation of Gynaecology and Obstetrics stage (<2C or >2C), histology (serous, clear cell, endometrioid or other), surgical status (suboptimal or optimal debulking) and chemotherapy received first-line (carboplatin with taxol or carboplatin alone). All patients were WHO performance status 0 or 1.

Clinical outcomes were evaluated for progression-free survival (PFS) and overall survival (OS), using data collected from patient records and follow-up data obtained from general practice records. PFS and OS were calculated from the date of histological diagnosis until radiological progression, according to Response Evaluation Criteria In Solid Tumours criteria or date of death, respectively. Individuals were censored according to last known follow-up with either the hospital or general practitioner.

Survival outcomes were calculated using Kaplan-Meier methodology and a log-rank test was used to compare differences in survival between trial and non-trial patients. A p value of ≤0.05 was deemed statistically significant. Data were analysed using GraphPad Prism (GraphPad Software V.4, San Diego, California, USA).

**RESULTS**

Sixty patients with ovarian carcinoma were evaluated; 30 were treated on trial and were matched with 30 patients who had received the same chemotherapy (carboplatin and paclitaxel or carboplatin alone) off trial. Patient baseline characteristics are shown in table 1.

The median PFS was 25.9 months in the trial group and 21.8 months for the control group. There was no difference according to PFS between the groups, (log-rank test: HR 0.87 (95% CI 0.48 to 1.54), p=0.6). The median OS was 68.9 months in the trial group and 64.3 months in the control group. No difference in overall survival was detected between the two groups (log-rank test: HR 0.87 (95% CI 0.46 to 1.64), p=0.7), figure 1.

<table>
<thead>
<tr>
<th>Table 1 Characteristics of patients with ovarian cancer</th>
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<tr>
<td><strong>Patient demographics</strong></td>
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<td>Age, years</td>
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<td>≤50</td>
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<td>51–70</td>
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<td>Histology</td>
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<td>Non-serous</td>
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<td>Surgery</td>
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<td>None</td>
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<td>Optimal debulking</td>
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<td>Carboplatin</td>
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DISCUSSION
Our study did not support the phenomenon of ‘trial effect’, at least not in a tertiary referral centre.

The lack of ‘trial effect’ may be attributable to a number of reasons. Settings where trials are routinely conducted with specialised teams working collaboratively with other (possibly international) centres (centre bias), and where teams are experienced in managing patients and adhering to strict guidelines (protocol effect), are likely to produce the best patient outcomes for both, trial and non-trial patients. Such centres tend to be relatively well resourced, with specialised nursing staff and supporting services (care effect), and may additionally attract motivated patients from better socioeconomic groups (placebo effect). Other ongoing trials or research and access to novel therapies, may additionally support services (care effect), and may additionally affect clinicians’ management plans and patients may change their behaviour by receiving care in such a setting (Hawthorne effect). It is, therefore, not unexpected that patients with characteristics similar to those on trial would have comparable survival outcomes if treated in a like environment. This has implications for the delivery of cancer care and for defining what constitutes the SOC.12 It is important to know whether patients should be treated only at tertiary referral centres with specialist expertise, access to a range of clinical trials and multicentre collaboration. Alternatively, it is important to ask whether oncology treatments can be delivered as effectively in less specialised settings as long as adequate specialist input is provided.

Our study is limited by its small sample size, retrospective nature and a number of confounding factors. However, given that the lower limits of the HR CIs are 0.468 and 0.4, respectively, for PFS and OS—an effect size representing a clinically relevant difference between groups—the possibility of a real trial effect should not be discounted altogether. Finding matched controls was difficult and limited the number of patients that could be included in the final analysis. Matching criteria were chosen based on prognostic value but these criteria were not comprehensive; we were unable to match cases and controls for other prognostic factors such as disease burden, lactate dehydrogenase and cancer antigen 125. In neither trial nor control group did we collect data on subsequent treatments that may have had a bearing on survival. Reassuringly, we did show that outcomes of patients with ovarian cancer at our centre are comparable with international standards.

If outcomes are better in tertiary centres of excellence with active research environments, it is necessary to ask, what are the essential components of these centres that need to be introduced to peripheral sites or is this indeed possible or cost effective? Patients may like the convenience of treatment closer to home but should be made aware that they may not receive the best care if local facilities are limited in specialist expertise.

Our study supports patient enrolment in clinical trials. The benefits of trial participation extend beyond their effects on individual trial entrants. There is a potential for providing best practice to all patients with cancer.

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.

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