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

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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 of patients to trials and organisation of oncology services.

Key questions

What is already known about this subject?

- Trial effect describes the phenomenon whereby patients receiving standard of care (SOC) as part of a clinical trial have superior survival compared to those on SOC off trial.
- Systematic reviews to date do not support trial effect but were performed before many SOC regimens were adopted.

What does this study add?

- It is the first cohort study performed in the era of modern therapy for patients with ovarian carcinoma.
- It does not support the phenomenon of trial effect in a tertiary centre.
- It highlights the need for more research into the differences (if any) of core components of care that patients receiving SOC treatment on clinical trials receive compared to those off trial.

How might this impact on clinical practice?

- Once defined, the core components or principles of care could be applied in all settings to promote the highest SOC for all patients regardless of centre of care.
- At the current time, participation in a trial even if a SOC arm is offered is still considered beneficial.

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 examples[1–4]—most randomised clinical trials (RCTs) do not produce positive outcomes. In a systematic review of 253 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*[6] first introduced the concept of the therapeutic misconception in 1982, clinician-researchers have been urged to avoid descriptions of their trials that may conflate 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,[7 8] 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,[9] ICON-5,[10] ICON-7,[11] from 2002 to 2008, were each matched with individuals who received the same first line 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 1 Characteristics of patients with ovarian cancer

Patient demographics	Trial N=30	Control N=30
Age, years		
<50	3	4
51–70	24	21
>71	3	5
Stage		
I/II	6	7
IIIA	2	2
IIIB	4	2
IIIC	18	19
Histology		
Serous	18	20
Non-serous	12	10
Surgery		
None	1	1
Suboptimal debulking	12	11
Optimal debulking	17	18
Treatment		
Carboplatin	10	10
Carboplatin and paclitaxel	20	20

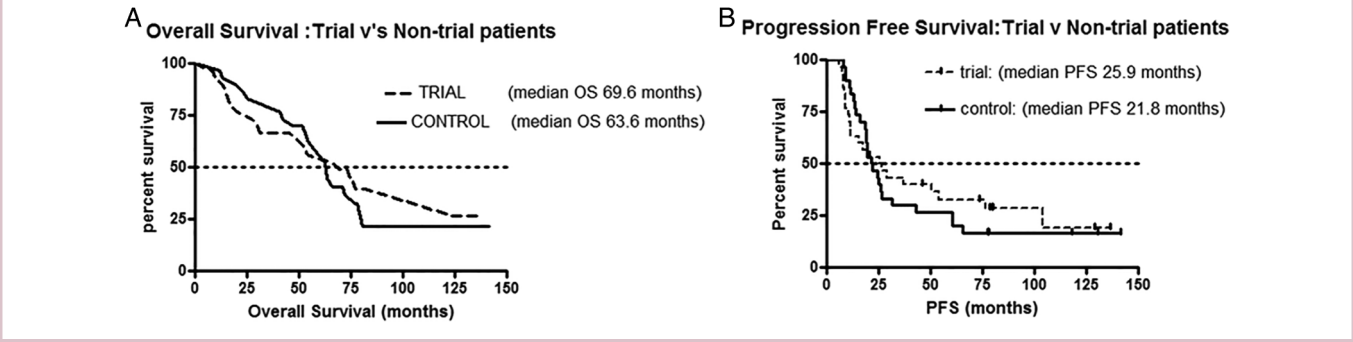

Figure 1 Kaplan-Meier curves comparing: (A) overall survival for patients treated on trial compared to those outside of a trial; (B) progression-free survival for patients treated on trial compared to those outside of a trial. OS, overall survival; PFS, progression-free survival.

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 in 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 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 they 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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REFERENCES

1. Hamid O, Robert C, Daud A, *et al*. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med* 2013;369:134–44.
2. Robert C, Ribas A, Wolchok JD, *et al*. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet* 2014;384:1109–17.
3. Chapman PB, Hauschild A, Robert C, *et al*. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011;364:2507–16.
4. Hodi FS, O'Day SJ, McDermott DF, *et al*. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711–23.
5. Gan HK, You B, Pond GR, *et al*. Assumptions of expected benefits in randomized phase III trials evaluating systemic treatments for cancer. *J Natl Cancer Inst* 2012;104:590–8.

6. Appelbaum PS, Roth LH, Lidz C. The therapeutic misconception: informed consent in psychiatric research. *Int J Law Psychiatry* 1982;5:319–29.
7. Peppercorn JM, Weeks JC, Cook EF, *et al*. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet* 2004;363:263–70.
8. Vist GE, Hagen KB, Devereaux PJ, *et al*. Systematic review to determine whether participation in a trial influences outcome. *BMJ* 2005;330:1175.
9. Banerjee S, Rustin G, Paul J, *et al*. A multicenter, randomized trial of flat dosing versus intrapatient dose escalation of single-agent carboplatin as first-line chemotherapy for advanced ovarian cancer: an SGCTG (SCOTROC 4) and ANZGOG study on behalf of GCIG. *Ann Oncol* 2013;24:679–87.
10. Bookman MA, Brady MF, McGuire WP, *et al*. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. *J Clin Oncol* 2009;27:1419–25.
11. Perren TJ, Swart AM, Pfisterer J, *et al*. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med* 2011;365:2484–96.
12. Krzyzanowska MK, Kaplan R, Sullivan R. How may clinical research improve healthcare outcomes? *Ann Oncol* 2011;22(Suppl 7): vii10–15.