Non-enrolment of ovarian cancer patients in clinical trials: reasons and background

P. Harter1*, A. du Bois1, C. Schade-Brittinger2, A. Burges3, K. Wollschlaeger4, M. Gropp5, B. Schmalfeldt6, J. Huober7, A. Staehle8 & J. Pfisterer9 for the Study Coordination Group of the AGO-OVAR†

1HSK, Dr Horst Schmidt Klinik Wiesbaden, Department of Gynaecology & Gynaecological Oncology, Wiesbaden; 2Marburg University, Coordination Centre for Clinical Trials, Marburg; 3University of Munich – Grosshadern, Department of Gynaecology & Obstetrics, Munich; 4Magdeburg University, Department of Gynaecology & Obstetrics, Magdeburg; 5EVK, Duesseldorf, Department of Gynaecology & Obstetrics, Duesseldorf; 6University of Munich r.d.I., Department of Gynaecology & Obstetrics, Munich; 7Tuebingen University, Department of Gynaecology & Obstetrics, Tuebingen; 8St Vincentius Hospital, Karlsruhe, Department of Gynaecology & Obstetrics, Karlsruhe; 9Universitätsklinikum Schleswig-Holstein Campus Kiel, Department of Gynaecology & Obstetrics, Kiel, Germany

Received 3 May 2005; revised 11 July 2005; accepted 11 July 2005

Background: Some retrospective analyses have suggested that participation in clinical trials is associated with better outcome. However, it is not clear to what extent selection bias contributes to this observation.

Patients and methods: We evaluated the reasons for non-enrolment of ovarian cancer patients in clinical trials. All patients with ovarian cancer not enrolled in clinical studies and treated in 2001 in the participating centres were documented retrospectively and compared with patients enrolled in clinical trials at the same institutions during the same time period.

Results: Two hundred and seventy-four patients with advanced ovarian cancer (FIGO stage IIB–IV) were included, of whom 139 (51%) and 135 (49%) patients were enrolled in this study and in prospective clinical trials, respectively. Ninety-four of 274 patients (34%) did not meet the inclusion criteria for clinical trials. Of 180 eligible patients, 28 (16%) refused participation and a further 17 patients (9%) were not recruited although they met the inclusion criteria. The non-study patients were older (66.7 versus 57.2 years; \( P < 0.0001 \)), underwent less radical surgery (hysterectomy, oophorectomy and omentectomy performed: 61.2% versus 80.7%; \( P = 0.001 \); rate of lymphadenectomy 30.9% versus 45.2%; \( P = 0.015 \)) and more frequently had bulky residual disease (residual disease >2 cm: 36.2% versus 20%; \( P = 0.016 \)). However, 62% of the non-study patients were treated with the same chemotherapy as in the standard arm of the respective clinical studies.

Conclusions: Study patients differ substantially from non-study patients, thus hampering generalisation of study results. Our results suggest that at least some inclusion criteria for clinical trials should be modified to increase study participation without compromising safety.

Key words: clinical trials, ovarian cancer, study participation, trial effect

Introduction

Randomised clinical trials are the ultimate tool for the evaluation of new treatment options and provide the evidence on which guidelines for routine care in oncology are usually based. However, study populations are in most cases selected cohorts, and therefore conclusions drawn from randomised trials are difficult to generalise [1–3]. So far, little attention has been paid to characterising the differences between study and non-study patients.

Retrospective analyses have shown participation in clinical trials to be associated with better clinical outcome [4, 5]. This phenomenon can easily be explained in positive trials when the experimental therapy shows superior results. However, this accounts only for the minority of phase III studies in oncology. For the remaining studies, it is unclear whether this effect is an epiphenomenon owing to a selection process, or whether study participation itself has a positive effect [6–10]. The latter might include a better quality of therapy for the individual patient or indicate a superior quality of care in hospitals participating in clinical trials, a fact that has been observed for ovarian cancer patients in Germany [5]. Better knowledge of the differences in both patient characteristics and actual treatment strategies between study and non-study patients might improve interpretation of study results in view of daily routine care. Furthermore, identification of reasons for not participating in clinical trials...
studies might provide tools to increase and broaden recruitment, thus making results more general and accelerating new therapy development.

Non-participation in clinical trials might be attributed to four main areas: (i) lack of information on the part of the patient and/or the treating physician; (ii) lack of resources; (iii) patients’ objections against trials; and (iv) selection processes. The latter, a matter of extensive discussion, could be caused by the respective inclusion and exclusion criteria [11, 12]. A study evaluating National Surgical Adjuvant Breast and Bowel Project trials suggested that inclusion/exclusion distinction be abandoned in favour of explicitly defined inclusion criteria. They also explicitly called for more research on the impact of criteria on generalisability [13]. It could also be owing to the physicians’ choice not to enrol patients who principally meet the inclusion criteria. Taylor et al. [14] published a study that looked at Eastern Cooperative Oncology Group (ECOG) investigators and found that all responding physician members (89%) had applied a systematic pattern of patient pre-selection for entry of clinical trials beyond the formal inclusion/exclusion trial criteria, and 83% defined randomisation and adherence to trial protocol as a serious challenge to their ability to make individualised treatment decisions. The present study focuses on quantitation of the following two complexes: (i) patients’ refusal of study participation; and (ii) selection processes in a cohort of patients treated in experienced study sites where a lack of information and resources can be ruled out.

**Methods**

We evaluated the reasons for non-enrolment of ovarian cancer patients in clinical trials at the 16 regional coordination centres of one of the largest European study groups in this area, the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group (AGO-OVAR). The hospitals used their own clinical tumour registries to identify patients treated for ovarian cancer in 2001. After the patients were identified, further information was obtained from their records. All of these centres retrospectively documented all patients with epithelial invasive ovarian cancer who were not enrolled in prospective clinical studies in 2001. Variables were patient characteristics, histology, grade and stage of disease, as well as details regarding surgical and medical therapy. This group of patients was compared with the group of patients enrolled in clinical studies by the coordination centres during the same time period. The data from these patients were extracted from the study database, avoiding an analysis of the original study objectives. The selection of the above-mentioned variables was based on the dataset of the prospective study (AGO-OVAR-7 comparing carboplatin–paclitaxel with carboplatin–paclitaxel–topotecan as first-line therapy in advanced ovarian cancer) running simultaneously in these centres [15]. Data were summarised by descriptive statistics. Frequency counts and percentages were used to describe categorical variables, and mean and range were used for continuous variables.

**Results**

Overall, 323 patients with primary invasive epithelial ovarian cancer were treated in the 16 coordination centres of the AGO-OVAR in 2001. Forty-nine patients with early ovarian cancer FIGO stages I–IIA were excluded from further analysis because in 2001 no study for this patient group has been recruited. The remaining 274 patients with ovarian cancer FIGO stages IIB–IV were analysed. Overall, 49% (135 patients) participated in clinical studies, and 51% (139 patients) were treated outside clinical trials (Figure 1). Of the 274 patients, 180 were eligible (66%). The participation rate of the eligible patients was 75%. The majority of the patients treated in prospective trials were enrolled in the prospectively randomised phase III AGO-OVAR-7 protocol (115 of 135 patients; 85%). The remaining 20 patients were enrolled in five further prospective studies in first-line therapy of ovarian cancer (so-called phase II pilot studies run concurrently by the AGO-OVAR and having comparable inclusion/exclusion criteria). Although they did not fail any inclusion criteria, of the 180 eligible patients 17 (9%) patients were not enrolled in a clinical trial owing to the physicians’ decision. Reasons for this decision could be provided for 16 of these patients and included age (10 patients), for which no upper limit was set in the AGO studies, and co-morbidities other than those defined in the exclusion criteria (six patients). Twenty-eight patients refused participation in a clinical study (Table 1). The latter group represented 20% of the 139 non-study patients and 16% of all 180 patients who met the inclusion criteria.

Of the 94 patients failing the inclusion criteria the most common item was glomerular filtration rate (GFR), which was defined with a lower limit of 60 ml/min. Forty-two patients (45%) had impaired renal function with a GFR <60 ml/min, of whom 43% had a GFR of 50–59 ml/min. Twenty-four patients (26%) had a history of a secondary malignancy (breast cancer, 12; colon cancer, four; endometrial cancer, two; non-Hodgkin’s lymphoma, two; renal cancer, two; bladder cancer, one; and non-small-cell lung cancer, one). The median observation time in the group of patients with secondary malignancies was 18.8 months (range 0–38), during which nine deaths were observed (37.5%). All nine patients died of ovarian cancer and not one experienced any relapse of her secondary malignancy. Another

![Figure 1](image-url)
24 patients showed a poor performance status (ECOG >2) or physicians estimated their life expectancy to be <6 months, both being exclusion criteria for AGO-OVAR-7. Nineteen patients had co-morbidities excluding them from participation in AGO-OVAR-7: 12 patients had a history of severe cardiac disease, four patients showed impaired liver function, two patients had neurological symptoms and one patient suffered from chronic hepatitis. Nine patients could not be enrolled because they had received their first cycle of chemotherapy at another hospital before continuing treatment at a study coordinating centre of the AGO-OVAR. Five patients did not understand the study design. The predefined interval between surgery and randomisation of 6 weeks or less had expired in the case of five patients. Overall, 51 of the 94 patients (54%) who did not meet inclusion criteria failed only one, and 43 patients (46%) two or more.

Comparison of all non-study patients with study patients revealed that non-participants were older (66.7 versus 57.2 years; \( P < 0.0001 \)) and had a poorer performance status (\( P < 0.001 \)). There was no difference with respect to FIGO-stage and other disease characteristics. The most commonly performed surgical procedures, including total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy, were performed less often in non-study patients compared with study patients (61.2% versus 80.7%; \( P = 0.0004 \)). Furthermore, retroperitoneal lymphadenectomy was performed in 30.9% of the non-study patients compared with 45.2% of the study patients (\( P = 0.015 \)). However, both cohorts had similar rates of bowel resection. Both the rates of macroscopically complete resection (34.8% versus 22.5%) and debulking to residual disease with maximum diameter of <2 cm (80% versus 63.8%) differed in favour of study patients (Table 2).

Information about systemic treatment was available for 137 of the 139 non-study patients. The standard chemotherapy applied in AGO-OVAR-7, carboplatin–paclitaxel, was administered to 85 of 139 non-study patients (61%). A further 28 patients (20%) were treated with platinum-based chemotherapy without taxanes, and eight patients (6%) received no platinum-based chemotherapy. Sixteen (12%) did not receive any chemotherapy. The application of the platinum–paclitaxel combination did not differ among patients failing inclusion criteria and patients not enrolled owing to the physician’s decision. Fifty-three (56%) of the 94 patients failing inclusion criteria received carboplatin–paclitaxel. Patients who were not enrolled owing to their physician’s decision received carboplatin–paclitaxel in 59% of cases. Patients who refused study participation were treated with carboplatin–paclitaxel in 79% of cases.

### Discussion

This retrospective analysis was performed at AGO-OVAR study coordinating centres, which are highly motivated to offer each eligible patient participation in prospective studies. The selection of coordinating centres limits interpretation to a highly select group of hospitals. However, this setting provides the advantage that reasons for non-participation might be free from non-medical aspects (e.g. economical or administrative reasons). Seventy-five per cent of the eligible patients did enter the clinical trial.}

### Table 1. Reasons for non-participation in clinical trials \((n = 139)\)

<table>
<thead>
<tr>
<th>Inclusion criteriaa</th>
<th>(n) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired renal function (GFR &lt;60 ml/min)</td>
<td>42 (45)</td>
</tr>
<tr>
<td>History of secondary malignancy</td>
<td>24 (26)</td>
</tr>
<tr>
<td>ECOG PS &gt;2 or life expectancy &lt;6 months</td>
<td>24 (26)</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>19 (20)</td>
</tr>
<tr>
<td>Chemotherapy started at another hospital</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Understanding the study</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Time from surgery to randomisation &gt;6 weeks</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Investigators’ decision</td>
<td>17 (9*)</td>
</tr>
<tr>
<td>Age</td>
<td>10 (59)</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>6 (35)</td>
</tr>
<tr>
<td>Participation refused</td>
<td>28 (16*)</td>
</tr>
</tbody>
</table>

aMultiple options possible.
bOf all patients \((n = 274)\).
cOf the eligible patients \((n = 180)\).
GFR, glomerular filtration rate; ECOG PS, Eastern Cooperative Oncology Group performance status.

### Table 2. Characteristics of non-study and study patients

<table>
<thead>
<tr>
<th></th>
<th>Non-study ((n = 139))</th>
<th>Study ((n = 135))</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years [mean (range)]</td>
<td>66.7 (37–87)</td>
<td>57.2 (24–81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>(64%)</td>
<td>(58%)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>0</td>
<td>44 (31.7)</td>
<td>58 (43.0)</td>
<td>(0.666)</td>
</tr>
<tr>
<td>1</td>
<td>63 (45.3)</td>
<td>68 (50.4)</td>
<td>(0.001)</td>
</tr>
<tr>
<td>2</td>
<td>21 (15.1)</td>
<td>9 (6.7)</td>
<td>(0.890)</td>
</tr>
<tr>
<td>3</td>
<td>9 (6.5)</td>
<td>-</td>
<td>(0.015)</td>
</tr>
<tr>
<td>4</td>
<td>2 (1.4)</td>
<td>-</td>
<td>(0.016)</td>
</tr>
<tr>
<td>TAH, BSO, omentectomy</td>
<td>85 (61.2)</td>
<td>109 (80.7)</td>
<td>(0.001)</td>
</tr>
<tr>
<td>Bowel resection</td>
<td>34 (24.5)</td>
<td>34 (25.2)</td>
<td>(0.016)</td>
</tr>
<tr>
<td>Lymphadenectomy</td>
<td>43 (30.9)</td>
<td>61 (45.2)</td>
<td>(0.012)</td>
</tr>
<tr>
<td>Residual disease</td>
<td>(0) mm</td>
<td>(47) (34.8)</td>
<td>(0.0004)</td>
</tr>
<tr>
<td>1–10 mm</td>
<td>40 (29.0)</td>
<td>42 (31.1)</td>
<td>(0.015)</td>
</tr>
<tr>
<td>11–20 mm</td>
<td>17 (12.3)</td>
<td>19 (14.1)</td>
<td>(0.001)</td>
</tr>
<tr>
<td>&gt;20 mm</td>
<td>50 (36.2)</td>
<td>27 (20.0)</td>
<td>(0.001)</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>-</td>
<td>(0.001)</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group performance status; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy.
a trial. This may be an acceptable rate, but nevertheless we need to investigate the reasons for non-participation in this group. Furthermore, we have to consider that only 180 patients (66%) of all patients with advanced ovarian cancer were eligible. Overall, only 49% of all patients were enrolled in a clinical trial. Similar participation rates have been reported by others in bladder cancer, sarcoma, small-cell lung cancer, ovarian cancer, multiple myeloma and breast cancer [6–8, 10, 12, 16–19]. Not only do these figures indicate that even in experienced study sites barriers to study participation exclude roughly half of the patients, but also that results of studies should possibly be generalised more cautiously than is commonly done. In the case of the latter it should be considered that the majority of patients excluded from trials showed different patient characteristics—in the present cohort, 34% of all patients did not meet the inclusion criteria, and an additional 9% of the eligible patients were judged unsuitable by the treating physician. Consequently, inclusion/exclusion criteria should be reconsidered, because some conditions making patients not eligible for study participation were obviously not included in the list of exclusion criteria. Unspecified exclusion factors might make interpretation of study results even more complicated. On one hand, exclusion criteria should be more specific and cover all conditions not allowing study inclusion. On the other hand, exclusion criteria might have been too rigorous, thus excluding patients who might have been suitable. This can be assumed for patients with a history of prior malignancies who represent a non-negligible proportion of patients. A recently performed survey in Germany indicated that 14% of all patients with epithelial ovarian cancer had a history of prior malignancies [20]. Our case number is too small and the observation period too short to prove that the impact of prior malignancy on the natural course of advanced ovarian cancer can be neglected. However, none of the nine deceased patients in this cohort died of their second malignancy and future trials should consider the inclusion of this group of patients. This approach would help to demonstrate that clinical studies are performed in the setting of clinical reality. Furthermore, this could create a balance between the necessity of fitting patient cohorts to trial design and designing trials according to patient needs. Stratification and pre-defined subgroup analysis could help to avoid possible bias. A similar discussion [21–25] has led to a better consideration of elderly patients in clinical trials in oncology. Reconsideration of exclusion criteria associated with safety parameters could be more difficult. However, one has to bear in mind that most of these criteria are arbitrarily defined and copied from one protocol to another. Furthermore, clinical reality forces every physician to offer treatment to patients presenting so-called exclusion criteria. The most common exclusion criteria in our cohort was the GFR, and most of the patients excluded owing to low GFR only failed the lower limit by 10–15%. However, if secondary neoplasms were allowed and the required GFR was decreased from 60 to 40 ml/min, a further 32 patients (18%) would have become eligible. This is a higher rate of patients than those refusing participation. Therefore, the subsequent clinical study was planned to evaluate whether broader inclusion criteria with respect to GFR was safe. We decreased the required GFR from 60 to 50 ml/min and planned an analysis comparing tolerability in patients with GFR of 60 ml or above and patients with GFR between 50 and 59 ml/min. Results of this prospective evaluation of lower GFR limits are pending.

A different group of patients is represented by those who refused study participation even though they met all inclusion criteria. In contrast to some other countries, study participation does not make any difference to the patients in Germany with respect to health-care costs. The standard therapy outside a clinical trial is funded by the public health-care system. This group accounted for approximately one in six patients (16%), but the number could be higher in centres that are not as trained in study methodology as the coordinating centres. We failed to prospectively document the reasons accounting for the individual decision to refuse participation. General refusal of randomisation or data collection, as well as the wish to be treated closer to home after surgery in a centre could be assumed to be the reasons. The latter could only be overcome by increasing the number of study centres. Refusal could possibly be reduced in some patients if more information were to be provided and specific education programmes were offered [26]. Six significant items have been identified by Wright et al. [27] correlating with participation in studies for oncology patients. Study entry was more likely when: (i) the patient perceived personal benefit; (ii) the decision was easy to make; (iii) the decision was made close to the time of study presentation; (iv) the patient did not expect to do well with standard therapy; (v) the physician believed the study was asking an important question; and (vi) the (Clinical Research Associate) (CRA) did not perceive significant side-effects.

Evidence for only partially defined selection processes could be seen in the analysis of surgical features. Later non-study patients were operated less radically and consequently finished the operation with a higher tumour burden. This adds to observed differences with respect to age and performance status, both of which were more favourable in study patients. Both surgical results and age/performance status are strong prognostic factors [28–30] and the observed differences strongly indicate the limitations when study results are translated to the general population [31]. These observations indicate that study results might be too optimistic and this accounts especially for the results of standard chemotherapy arms that are usually used to counsel patients about prognoses and benefits from specific treatment modalities outside of trials.

This AGO-OVAR trial provides some interesting insight into possible limitations of translating study results in clinical routine and treatment recommendations. However, retrospective evaluation limits our analysis to ‘objective’ factors. Consequences have already led to modification of inclusion and exclusion criteria in subsequent trials. Furthermore, a planned prospective trial will evaluate the individual reasons for refusing study participation in a more detailed way.

Acknowledgements

The authors thank the AGO-OVAR staff of the study offices in Kiel and Wiesbaden and the statistical department in Marburg.
None of the authors declared any conflict of interest in the present study.

The following additional investigators/centres contributed to the study (in alphabetical order): A. Belau (Greifswald University), U. Canzler (Dresden University), C. Jackisch (Marburg University), R. Kimmig (Essen University), S. Loibl (Frankfurt University), H. J. Lueck (MIHH Hannover), W. Schröder (Bremen Zentralkrankenhaus) and J. Sehouli (Berlin University Charite).

References