Clinical factors of response in patients with advanced ovarian cancer participating in early phase clinical trials

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Abstract
Drug resistance to conventional anticancer therapies is almost inevitable in patients with advanced ovarian cancer (AOC), limiting their available treatment options. Novel phase I trial therapies within a dedicated drug development unit may represent a viable alternative; however, there is currently little evidence for patient outcomes in such patients. To address this, we undertook a retrospective review of patients with AOC allocated to phase I trials in the Drug Development Unit at Royal Marsden Hospital (RMH) between June 1998 and October 2010. A total of 200 AOC patients with progressive disease were allocated to ≥1 trial each, with a total of 281 allocations. Of these, 135 (68%) patients commenced ≥1 trial (mean 1.4 [1–8]), totaling 216 allocated trials; 65 (32%) patients did not start due to deterioration resulting from rapidly progressive disease (63 patients) or patient choice (2 patients). Response Evaluation Criteria in Solid Tumours (RECIST) complete/partial responses (CR/PR) were observed in 43 (20%) of those starting trials, including those on poly(ADP-ribose) polymerase (PARP) inhibitors (18/79 [23%]), antiangiogenics (9/65 [14%]) and chemotherapy combinations (14/43 [33%]). Factors associated with CR/PR included: fewer prior treatments, platinum-sensitive disease, CR/PR with prior therapy, (the United States-based) Eastern Cooperative Oncology Group (ECOG) performance status score, fewer metastatic sites, higher albumin and haemoglobin levels, lower white cell counts and baseline CA125 levels, germline BRCA1/2 mutations and better RMH Prognostic Score. Mean survival was 32° months for patients who achieved CR/PR. Treatments were generally well tolerated. Most patients with AOC (134/200 [67%]) received ≥1 subsequent line of therapy after phase I trials. Our data suggest that phase I trial referrals should be considered earlier in the AOC treatment pathway and before the onset of rapid disease progression particularly with the emergence of promising novel agents in the era of precision medicine.

1. Introduction

Ovarian cancer is the fifth most common malignancy in the United Kingdom (UK), with more than 7000 women diagnosed each year [1]. The majority of patients are diagnosed with advanced stage disease, and despite good initial responses to standard chemotherapy regimens, most will inevitably develop drug resistance leading to disease progression. For such women, phase I trials represent an opportunity to access new anticancer treatments that are at early stages of clinical development, which would otherwise be inaccessible to them. However, such novel agents come with limited knowledge of their toxicity profile or antitumour activity. This has been one of the main reasons for the historically low referral rates of patients with advanced ovarian cancers (AOCs) to specialist phase I clinical trial units, in contrast to other malignancies. Yet in recent years, a number of drugs have been developed to inhibit targets or pathways known to be critical drivers of ovarian cancer, leading to increased phase I trial referrals for such patients [2]; [3]; [4]; [5]; [6]; [7] ; [8].

There are several factors that have been established as predictors of response to further chemotherapy, and overall prognosis. Arguably, the most important of these historically is the platinum chemotherapy status, with patients defined as platinum-sensitive demonstrating improved anticancer responses to chemotherapy and longer overall survival (OS) compared with patients with platinum-resistant disease. The platinum status has also been demonstrated to influence response rates to molecularly targeted agents, such as poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors, where early studies of olaparib showed response rates of 69% in those with platinum-sensitive disease, compared with 45% and 23% in the platinum-resistant and refractory cohorts respectively [9]. Recent studies have investigated the role of somatic aberrations in ovarian cancer oncogenesis, with each histological subtype demonstrating distinct patterns of genomic abnormality prevalence within different pathways [10]; [11]; [12]; [13]; [14]; [15]; [16]; [17]; [18]; [19] ; [20]. This molecular heterogeneity offers potential therapeutic targets for novel molecularly targeted agents in patients with AOCs beyond the current standard chemotherapeutic options [21].

Data on treatment outcomes for patients with AOCs participating in early phase clinical trials are currently limited. We therefore reviewed our experience of patients with AOCs referred for consideration of early phase clinical trials in the Phase I Drug Development Unit at the Royal Marsden Hospital, London, United Kingdom. The primary objective was the identification of predictors of clinical benefit. Secondary objectives included the assessment of toxicity and antitumour activity of such experimental trial agents in our series of patients. Herein, we report our findings of the treatment outcomes for our patients, together with independent indicators of response.

2. Patients and methods

We conducted a retrospective review of the electronic patient records (EPR) of all patients with AOCs (or fallopian tube or primary peritoneal malignancies), treated on one or more phase I clinical trials within the Drug Development Unit at the Royal Marsden NHS Foundation Trust between June 1998 and October 2010. Data on patient follow-up were collected until death or censored at June 2013, whichever was earlier. This retrospective study and all clinical trials included within it were approved by the Royal Marsden Research and Development Committee; and all patients had provided their written informed consent prior to enrolment onto their respective clinical trial. Allocation to a clinical trial for all patients was made after consideration of individual clinical, radiological and laboratory data. Several phase I trials had specific mandatory eligibility criteria such as the presence or absence of germline genetic mutations. If the patient was eligible for more than one phase I trial, allocation was made based on patient preference and/or physician choice. At

disease progression, a number of patients went on to be treated on further Phase I trials within the time assessed. Each allocation to a new Phase I trial was treated as a separate treatment event.

All patients underwent baseline assessments before allocation and enrolment, including medical history, physical examination and laboratory tests as per trial protocol. The interval between allocation and study commencement was typically 3–4° weeks, during which time screening was performed according to specific protocols. After commencing on study, patients were reviewed regularly as per protocol. At each visit, detailed history and physical examination were performed, together with blood tests. Toxicities were assessed, graded and considered for their relationship to study drug, with appropriate dose adjustment for toxicity if necessary. All patients had radiological review at baseline, following 2 cycles, and then as defined by the trial protocol. Radiological antitumour response was reported using Response Evaluation Criteria in Solid Tumours (RECIST) 1.0 or 1.1, as defined by the specific trial protocol. The Gynaecologic Cancer Intergroup (GCIG) cancer antigen 125 (CA125) response was also assessed in patients with detectable levels of CA125 tumour marker. Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or at the discretion of the treating clinician.

2.1. Data collection

The EPR was reviewed for each patient and the following data were collected for each patient: age at diagnosis, stage, grade, histological subtype, tumour oestrogen receptor status, molecular profiling if undertaken, germline BRCA1/2 mutation status, previous lines of anticancer therapy (drugs, dates and duration of treatment and best response), platinum chemotherapy status, ECOG performance status, number of metastatic sites, presence or absence of visceral metastases, haematological parameters, albumin, CA125 and date of death or last follow-up.

2.2. Response assessments

Radiological responses were assessed using RECIST criteria every 2–3 cycles of therapy according to the trial protocol. A RECIST partial response (PR) was defined as ≥30% decrease in the sum of the largest diameter of target lesions, with a RECIST complete response (CR) occurring in those with disappearance of all target lesions. RECIST progressive disease (PD) was defined as a ≥20% increase in the sum of the longest diameter of target lesions. RECIST stable disease (SD) was defined as neither sufficient shrinkage to meet PR criteria, nor sufficient growth to meet PD criteria, while prolonged RECIST stable disease was defined as SD for at least 4°months.

GCIG CA125 response criteria are defined as ≥50% decrease in CA125 levels compared to pre-treatment levels, and the response must be confirmed and maintained for at least 28°d. Only patients with a CA-125 level of ≥2 × upper limit of normal within 2°weeks prior to commencing treatment were evaluable by GCIG CA125 criteria. Patients were also stratified by their platinum status. Patients were considered platinum sensitive if their disease progressed >6°months after completing platinum-based chemotherapy, platinum resistant if their disease progressed <6°months after completing platinum-based chemotherapy; and platinum refractory if their disease progressed while on platinum chemotherapy.

The Royal Marsden Hospital (RMH) prognostic score was calculated as follows: albumin <35 g/l, lactate dehydrogenase (LDH) > upper limit of normal (ULN); and the presence of >2 sites of metastases all scored 1 point each; while albumin ≥35 g/l, LDH <ULN and the presence of 2 or fewer sites of metastases each scored 0 points. Patients with an RMH score of 0 or 1 were considered good prognosis; while those with an RMH score of 2 or 3 were considered of poorer prognosis.

Overall survival was measured from the date of starting treatment on the Phase I trial until death from any cause or last follow-up. Trial duration was measured from the day of starting treatment, until the last dose of treatment.

2.3. Statistical considerations

The demographic and clinical characteristics of patients were summarised using descriptive statistics. The association between categorical variables and responses was assessed using the Fisher's exact test. Multivariate analysis was used to identify predictors of response.

3. Results

A total of 200 patients with AOCs were allocated to at least one phase I trial, with 281 allocations included between June 1998 and October 2010. The majority of patients had high-grade serous tumours (129/200; 64.5%), with other histological subtypes including carcinosarcomas, granulosa cell tumours and undifferentiated ovarian cancer. Patients mainly had either platinum-resistant or refractory disease (145/200; 72%), with the rest harbouring platinum-sensitive disease (55/200; 28%). The median age of the patients was 51°years (range 20–73°years). The median number of prior systemic anticancer treatments was 4 (range 1–14). One-hundred and thirty-five patients started at least one phase I trial, for a total of 216 trial allocations. As many as 65 of 200 (32%) did not begin their allocated trial, due to interval disease progression (63/65 [97%] patients) or patient choice (2/65 [3%] patients). The median time from trial allocation to commencement of treatment was 23°d (range 1–64°d). Germline BRCA1/2 mutation status was known in 62/200 (31%) patients (of which 53/62 [85%] patients had BRCA1/2 mutations, 9/62 [15%] patients were BRCA1/2 wild type), and BRCA status was unknown in 138 patients. The entry to two of three PARP inhibitor trials was based on the presence of a pathogenic BRCA1/2 mutation. The patient allocation to all other trials was not based on mutation status. Full demographic data are detailed in Table 1.

3.1. Phase I clinical trials

The phase I trials included in this study were classified into 11 groups based on the underlying mechanism of action of the investigational agent: (1) PARP inhibitors, (2) antiangiogenic agents, (3) histone deacetylase (HDAC) inhibitors, (4) heat shock protein 90 (HSP90) inhibitors, (5) phosphatidylinositol-3 kinase (PI3K) inhibitors, (6) c-MET inhibitors, (7) insulin growth factor-1 receptor (IGFR) inhibitors, (8) chemotherapy/targeted therapy combinations, (9) targeted therapy combinations, (10) radiotherapy/targeted therapy combinations and (11) RAS/RAF/MEK/ERK inhibitors and others.

Overall, 35/135 (26%) patients achieved objective antitumour responses in at least one trial, including 1 RECIST CR and 34 RECIST PR. Prolonged stable disease >4°months was observed in a further 21 patients, for an overall patient clinical benefit rate (CBR) of 56/135 (41%). The mean trial duration was 5.8°months (0.35–53°months). Two patients had a RECIST PR to their initial phase I trial therapy and prolonged RECIST stable disease on their subsequent phase I trial. By patient trial allocations, there was an anticancer response rate of 35/216 (16%), and an overall CBR of 58/216 (27%). Mean OS was 32°months for RECIST CR/PR pt v 3.2°months, for patients who did not start treatment due to PD ($p < 0.0001$).

3.2. Baseline clinical factors of antitumour response

We assessed a range of baseline clinical factors to ascertain whether they differed significantly between patients who responded versus those who did not start treatment due to progressive

disease. We identified multiple clinical factors through multivariate analysis that differed between these two groups, many of which correlated with patients with heavy disease burdens, or those who were heavily pre-treated with prior chemotherapy regimens (Table 2). Women with platinum-sensitive disease were more likely to start a phase I trial than those with platinum-resistant or refractory disease ($p = 0.0016$). Those with platinum-sensitive disease were also more likely to respond to their phase I trial therapy ($p < 0.0001$). The presence of a germline BRCA1/2 mutation was also an indicator of antitumour response across all treatment categories ($p < 0.0001$). The mean RMH prognostic score was also significantly different between responders versus those with progressive disease ($p < 0.0001$).

3.3. Individual phase I trial outcomes

3.3.1. PARP inhibitors

Seventy-eight patients with AOCs were allocated to 1 of 3 PARP inhibitor trials with 63 patients beginning treatment. RECIST responses occurred in 18 patients (28.5%), with a median duration of response of 21 months (range 4.5–75 months). A further 13 patients experienced prolonged RECIST stable disease, for a clinical benefit rate (CBR) of 49%. Patients with a BRCA1/2 germline mutation had a higher RECIST response rate than those with unknown BRCA1/2 mutation status (16/47 [34%] versus 2/16 [12%], $p < 0.0001$), as did those with platinum-sensitive disease (11/24 [46%] versus 7/39 [18%], $p = 0.039$). The median time to progression among all patients was 4°months (range 1.3–75).

3.3.2. Antiangiogenic agents

A total of 64 patients were allocated to treatment with 1 of 5 antiangiogenic drugs, of which 42 began treatment. There were 9 RECIST responses (21%), and 10 patients with stable disease >4° months, for a CBR of 45%. There were 22 patients allocated to an antiangiogenic agent who did not start treatment due to disease progression. There was a higher response rate amongst those who were platinum-sensitive ($p < 0.0001$), but no other features were noted to predict response.

3.3.3. PI3K-AKT pathway inhibitors

There were 32 patients allocated to treatment with drugs targeting the PI3Kinase pathway, with all patients being platinum-resistant at the time of entry to the trial. More than half of the patients allocated (56%) did not begin treatment, due to interval disease progression. There were no RECIST responses seen, although 2 patients (14%) had prolonged stable disease.

3.4. Molecularly targeted agent and chemotherapy combinations

There were six trials assessing the combination of chemotherapy (platinum or taxane), combined with a targeted agent, with a total of 43 patients allocated to treatment, 32 of whom began treatment. There were RECIST responses in 14 patients (44%), with SD > 4 months in a further 3 patients, for a CBR of 53%. These treatments had higher rates of toxicity, with 4 patients (12.5%) withdrawing from treatment after the first cycle due to neutropenic sepsis. The patients with platinum-sensitive disease had significantly higher response rates, irrespective of the chemotherapy agent used (50% versus 25%, $p = 0.0001$).

3.4.1. Other early phase clinical trials

There were small numbers of patients treated with each of the remaining classes of drugs. There was only 1 other PR (RECIST) noted, in a patient treated with a combination of 2 targeted agents. The full details are shown in Supplementary Table 1.

3.5. Systemic therapies after phase I trials

There were 142 patients (71%) who went on to receive at least one further line of systemic treatment after their phase I trial, with 82 patients (41%) receiving two or more further lines of treatment. The full list of subsequent treatment is shown in Table 3.

3.6. Trial-related toxicities

The patients treated on the phase I trials generally tolerated treatment well, with the majority of reported toxicity either Grade 1 or Grade 2 (332, 90%). This was generally managed with a dose reduction or treatment interruption. There were 36 Grade 3/4 toxicities. All of the Grade 4 toxicity occurred in patients treated on the chemotherapy/targeted agent combination treatments. There were no Grade 5 toxicities. The full toxicity data are shown in Table 4.

4. Discussion

Our experience represents one of the largest reported cohorts of ovarian cancer patients treated within phase I trials. Our report covers a wide range of phase I trials, from early combined chemotherapy/novel agent combinations, through to recent dual targeted agent trials, reflecting the emergence of targeted treatment, and the increasing interest in ovarian cancer as a tumour with a number of potentially targetable pathways. This has led to the development of drugs such as bevacizumab, which have resulted in significant improvements in outcome for patients at multiple points in the treatment pathway [22]; [23]; [24] ; [25]. The time period (1998–2010) also included the first trials of PARP inhibitors in ovarian cancer patients. The first of these, olaparib, has received EU and FDA approval and is available in a number of countries as an option for maintenance treatment in woman following platinum sensitive relapse. Studies are ongoing for other PARP inhibitors, including a wider range of indications [26]; [27]; [28]; [29] ; [30].

The majority of the ovarian cancer patients referred for phase I trials in our series were heavily pre-treated. This is in keeping with studies such as Brunetto et al., who reported that one of the most common reasons for referral to phase I units in colorectal cancer patients was exhaustion of conventional chemotherapeutic options [31]. Despite this, 41% of patients in our series went on to have multiple further lines of systemic treatment, with either phase I agents or other agents. This is contrary to the widely perceived notion of phase I trials as the ‘final option’ for such patients.

One of the most striking features of our study was the number of patients allocated to a trial, but who had rapid progression of disease, rendering them ineligible. This was most commonly due to deterioration in their performance status or development of new metastatic disease that impacted upon haematological parameters. In our study, we identified a number of factors that differed significantly between patients with rapidly progressive disease and those who responded to treatment; and further validated the RMH prognostic score as a discerning factor in identifying those who may benefit from phase I trials [32] ; [33]. In general, these factors were all indicative of a greater burden of disease, such as number of metastatic sites, baseline albumin and CA-125 levels and ECOG status. This suggests that many patients were referred at a point in their disease process where they were unable to benefit from such targeted agents, many of which have a cytostatic, rather than cytocidal effect. Such patients were also at risk of common ovarian cancer complications, such as bowel or gastric outlet obstruction, limiting the use of orally administered agents. In contrast, those with other established predictors of response, such as platinum sensitivity and fewer prior lines of therapy were more likely to respond to their phase I trial. We therefore suggest that the optimal timing to consider phase I trials may be earlier in the patient's journey,

before they have exhausted all standard chemotherapeutic options. Such patients are not only generally in better physical shape, able to withstand potentially unexpected side-effects, but also have the option of commencing alternative systemic treatments if they do not respond to their phase I trial agent.

There is increasing interest in routine molecular testing of all patients considering phase I trials, so that germline and somatic mutation data can be incorporated into trial selection [34]. This molecular matching of target and agent has been reported to significantly improve both progression-free survival (3.9 versus 2.2° months), and median survival (11.4 versus 8.6° months) compared to unmatched therapy [35]. Matched therapy was also associated with a higher objective response rate of 12%, compared with only 5% in those with unmatched cohorts. In our cohort, dating back to 1998, only patients entering two of three PARP inhibitor trials were selected for presence of a pathogenic BRCA mutation, with no other molecular matching performed at that time. With improvements in technology, molecular profiling for targetable mutations is now offered to all suitable patients in our Phase I unit, to maximize patient benefit from treatment. Despite this, many patients still do not have therapeutically targetable mutations, limiting the benefit of this strategy.

We did not observe any responses in the 14 patients treated with agents targeting the PI3 kinase pathway, with only 2 patients demonstrating prolonged stable disease. This contrasts with other studies that have reported responses with these agents in patients with AOC [36]. PIK3CA mutations are relatively common, reported in 20% of endometrioid ovarian cancer, and up to 33% of clear cell patients [11]; [15] ; [37]. Amplification of PIK3CA is reported in 40% of high grade serous patients [11]. Although we do not have specific mutation information on the patients treated, all were high grade serous or clear cell patients, making it likely that patients with alterations in this pathway were represented in this cohort. However, all of the patients treated had platinum-resistant/refractory disease. This was a predictor of response across other treatment groups, and it is possible this may have impacted on the response rates. It is also notable that we did not collect dosing information, and therefore these patients may not have received sufficient drug to see efficacy.

There are several limitations to our study. This was a retrospective study, with an under-representation of clear cell and endometrioid histologies; and an over-representation of rare subtypes, such as small cell ovarian carcinoma. There was also a significant proportion of undifferentiated carcinoma, which in part reflects the time period during which patients were diagnosed. Another limitation of the study is the reported toxicity, which was based on retrospective collection of data. Each phase I patient had toxicity recorded and graded with every visit, but concurrent dose levels were not collected, thereby limiting interpretation of these data.

Our study has demonstrated that ovarian cancer patients do benefit from phase I trials, with objective response rates of 26% in those starting treatment. This response rate was higher in those with platinum-sensitive disease, most of whom were treated at an earlier stage in their disease pathway than those with platinum-resistant or refractory disease. Many of our patients went on to receive multiple lines of treatment after their phase I trial, including both other phase I drugs and further chemotherapy. This response rate may improve further with the use of routine molecular profiling, and matching of therapy. We propose that patients may benefit from a more collaborative approach, with early review by a phase I unit. Such patients could undergo molecular profiling early, with the aim of moving to an appropriate phase I trial earlier, while maintaining the option of further chemotherapy or other clinical trials to widen their treatment options.

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Table 1. Patient demographics.

Demographic	Variable	No. of patients (%)
Age	<40	23 (11.5%)
	40–49	60 (30%)
	50–59	72 (36%)
	60–69	41 (20.5%)
	≥70	4 (2%)
Tumour histology	Serous	129 (64.5%)
	Clear cell	6 (3%)
	Endometrioid	3 (1.5%)
	Mucinous	6 (3%)
	Mixed	8 (4%)
	Undifferentiated	27 (13.5%)
	Carcinosarcoma	6 (3%)
	Granulosa cell	5 (2.5%)
	Other	10 (5%)
Prior lines of treatment	1	20 (10%)
	2	33 (16.5%)
	3	45 (22.5%)
	4	36 (18%)
	5–6	47 (23.5%)
	7–8	13 6.5%)
	9+	6 (3%)
Platinum status	Sensitive	51 (25.5%)
	Refractory/resistant	145 (72.5%)
	Not Recorded	4 (2%)
Visceral metastases	Present	85 (42.5%)
	Absent	115 (52.5%)
ECOG performance status	0	45 (22.5%)
	1	142 (71%)
	2	10 (5%)
	>2	3 (1.5%)

Table 2. Potential predictors of response to phase I trial therapies.

Factor assessed	p value
No. prior lines of treatment	p = 0.02
Mean albumin (g/l) at baseline	p < 0.001
No. metastatic sites	p = 0.04
Mean RMH score	p < 0.001
RECIST response to preceding treatment	p < 0.001
ECOG status at baseline	p = 0.02
Baseline haemoglobin	p < 0.001
Baseline CA-125	p = 0.02
Baseline LDH level	p = 0.43
Baseline platelet level	p = 0.11
Baseline neutrophil level	p = 0.32
Baseline creatinine level	p = 0.14

Table 3. Post phase I trial systemic antitumour therapies.

No. of subsequent treatments	No. of patients (%)
0	58 (29%)
1	60 (30%)
2	42 (21%)
3	18 (9%)
4	7 (3.5%)
5	4 (2%)
7	2 (1%)
Not recorded	7 (3.5%)
Still on phase I trials[a]	2 (1%)

[a] As of 30th June 2013.

Table 4. Reported drug-related toxicities.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	85	29	12 (6[a])	
Nausea	45	19	1 (1[a])	
Vomiting	14	6		
Dyspepsia	8	1		
Rash	12		5	
Diarrhoea	29	6	3	
Constipation	11	7		
Anorexia	11	6		
Neutropenia	3	5	1 (1[a])	
Anaemia	1	3	1 (1[a])	
Thrombocytopenia	2	4	4 (2[a])	
Neutropenic sepsis				4 (4[a])
Non-neutropenic infection		2	1	
Hypertension	3	2	1	
Abdominal pain	4	4	1 (1[a])	
VTE		1		
LFT changes	2		2	
Oedema	5	2		

[a] Denotes G3/4 toxicity observed in chemotherapy combination trial. VTE: Venous thromboembolism; LFT changes: elevated liver enzymes during chemotherapy