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Original Research

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

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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 [2–8].

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 [10–20]. 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