Original Articles

A prospective randomised phase II trial of thalidomide with carboplatin compared with carboplatin alone as a first-line therapy in women with ovarian cancer, with evaluation of potential surrogate markers of angiogenesis

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Summary

Objectives: To compare the safety and efficacy of thalidomide in combination with carboplatin to carboplatin alone as a first-line therapy in women with ovarian cancer and to evaluate the anti-angiogenic effects of thalidomide by measurement of surrogate markers of angiogenesis. *Methods:* Forty patients with Stage IC-IV ovarian cancer were randomly assigned to receive either carboplatin (AUC 7) intravenously every four weeks for up to six doses (n = 20) or carboplatin at the same dose and schedule, plus thalidomide 100 mg orally daily for six months (n = 20). *Results:* After median follow-up of 1.95 years, there was no difference in the overall response rate (90% in carboplatin arm, 75% in combination arm; $p = 0.41$). Increased incidence of symptoms of constipation, dizziness, tiredness and peripheral neuropathy was observed in the combination arm. There was a significant fall in CA-125 and E-selectin in both arms after treatment and VCAM-1 in the carboplatin arm. No significant difference between the two arms was observed in any of the markers analysed. *Conclusions:* In our trial the addition of thalidomide to carboplatin was well tolerated with no increased efficacy. The fall in some of the angiogenic markers in both groups may reflect tumour response rather than any specific anti-angiogenic effect of thalidomide.

Key words: Angiogenesis; Carboplatin; Ovarian cancer; Phase II trial; Thalidomide.

Introduction

Ovarian cancer is the fourth most common cancer among women in the UK with around 6,900 new cases diagnosed each year. The majority of patients present with advanced disease (Stage III/IV) and primary treatment is usually optimal debulking surgery followed by chemotherapy with carboplatin ± paclitaxel, which typically produces a response rate of around 60-70% [1, 2]. Despite advances in treatment, most patients die from recurrent disease, with about 30% surviving five years after diagnosis [3]. Hence, there is a major need for new approaches to the treatment of this common gynaecological cancer.

Angiogenesis, the formation of new blood vessels, is required for most tumours to grow beyond 1-2 mm in diameter. The expression of platelet-derived growth factor, an angiogenic agent, was shown to be greater in malignant ovarian tumours than benign tumours ($p < 0.001$) [4] and increased VEGF expression was observed in 97% of ovarian carcinomas, and strong expression was associated with advanced stage and poorer survival [5]. Tumour derived VEGF is also obligatory for ascites formation in ovarian cancer patients [6]. Elevated pre-treatment serum VEGF levels in ovarian cancer patients have been shown to be associated with poorer disease-free survival and overall survival [7, 8]. Other circulating angiogenic factors like basic fibroblast growth factor (bFGF), E-selectin, von Willebrand factor (vWF) and vascular cell adhesion molecule-1 (VCAM-1) have been found to be elevated in patients with many solid tumours including ovarian cancer [9-12].

Thalidomide is an immunomodulatory agent that inhibits angiogenesis and cytokines such as tumour necrosis factor [13, 14]. In addition it has been shown to modulate cell adhesion [15]. Thalidomide has been demonstrated to have modest activity in several human tumours including ovarian cancer [16]. There was no previous published report of a combination of thalidomide with chemotherapy in ovarian cancer when this trial was designed. Recent studies using single agent thalidomide at the median dose of 200 mg/day in advanced and recurrent ovarian cancer showed the response rate varied from 7.7% to 18% and stable disease in 35%-53.8% of patients [17, 18]. Many phase I and II trials using thalidomide in incremental doses in combination with carboplatin in solid tumours support further investigation of this combination [19, 20].

We initiated an open label, prospective, randomised phase II study of carboplatin and thalidomide in chemotherapy naive patients with Stage IC-IV epithelial ovarian cancer. The primary objectives were to investi-

Revised manuscript accepted for publication September 30, 2010

gate safety and efficacy of thalidomide in combination with carboplatin and to assess the anti-angiogenic effects by surrogate markers. The effective dose of thalidomide in solid tumours is not known. It is not clear if a definite dose response relationship exists, or whether smaller doses of thalidomide can be equally effective with fewer side-effects. There is also concern about peripheral neuropathy, particularly when the dose of thalidomide exceeds > 75 mg/day [21] and there is some correlation between cumulative dose of thalidomide and risk of peripheral neuropathy [22, 23]. The information regarding the neurotoxicity of thalidomide precluded the use of thalidomide beyond a total dose of 18 g when the trial was designed. Since thalidomide was planned to be given for a total duration of six months, we decided to use a dose of 100 mg/day as continuous therapy, with the total cumulative dose of 18 g. The combination of carboplatin and paclitaxel with thalidomide was not chosen in view of concern regarding the increased risk of peripheral neuropathy associated with the above combination. Increasing carboplatin doses above AUC 7 doses not necessarily improve the likelihood of response but does increase myelotoxicity [24]. Therefore we decided to use carboplatin at the dose of AUC 7 given every four weekly, based on EDTA clearance, which was standard dosing in our unit at the time the trial was designed.

Materials and Methods

The study was conducted after local ethical research committee approval and according to Helsinki's declaration (1989). All newly diagnosed eligible ovarian cancer patients were recruited after written informed consent when they attended oncology outpatient clinics. To be eligible, each patient was required to meet the following criteria: (1) histologically confirmed diagnosis of epithelial ovarian cancer with Stage IC-IV; (2) WHO performance status 0, 1 or 2; (3) age over 18 years. To avoid potential teratogenicity from thalidomide all eligible ovarian cancer patients should be postmenopausal or if premenopausal, they must have had bilateral salpingo-oophorectomy and/or total abdominal hysterectomy. Patients who received previous chemotherapy for ovarian cancer were ineligible. Patients with diabetes mellitus, chronic neurological disease causing peripheral neuropathy and other concurrent invasive malignancies were excluded. All patients were given at least 24 hours before they could make the final decision about the study. This study was conducted in the Cancer Research UK Medical Oncology Unit, Churchill Hospital, Oxford and St. James's University Hospital, Leeds.

Treatment plan

Patients were randomised without stratification to receive either (1) carboplatin alone at the dose of AUC 7 {7 x (creatinine clearance + 25)} using creatinine clearance calculated by EDTA clearance (uncorrected value) every four weeks up to six cycles; or carboplatin at the same dose and schedule, plus thalidomide 100-mg orally each day at bedtime. Thalidomide was taken continuously for a total of 24 weeks commencing on the first day of carboplatin therapy and stopped four weeks after the last dose of chemotherapy. All patients received standard premedications before the chemotherapy. Prior to each cycle of chemotherapy biochemistry and haematological tests were obtained. Serum CA-125 was measured before each cycle. All patients had a baseline CT scan of the abdomen and pelvis with or without chest and the scan was repeated after three cycles of chemotherapy and at the end of treatment to assess response.

Sensory nerve action potentials (SNAP) were performed in all patients prior to treatment and then at two, four and six months. Thalidomide was discontinued if there was a greater than 40% decrease in the sensory nerve action potential when compared with the baseline value. If the decrease was less than 40%, then the test was repeated after one month.

Toxicity and response evaluation

Toxicity was defined by Cancer and Leukaemia Group B (CALGB) expanded common toxicity criteria. Carboplatin was delayed by one week if absolute neutrophil count was less than 1.5 x 10^9/l or platelets were less than 100 x 10^9/l. If the treatment was delayed by two or more weeks then the dose of carboplatin was reduced to the dose of AUC 5. If grade 3 or 4 myelosuppression occurred the dose of carboplatin was reduced to AUC 5. If the calculated creatinine clearance worsened by more than 25%, then EDTA clearance was repeated and the dose of carboplatin was recalculated. For those patients with evaluable or measurable disease, WHO criteria were used to assess response after completion of treatment.

Assessment of surrogate markers of angiogenesis

Prior to each cycle of treatment, two 10-ml blood samples for serum and plasma were obtained to analyse potential surrogate markers of angiogenesis. The blood samples were centrifuged at 2500 rpm for 10 min at 4°C and separated plasma and serum were stored at –20°C or below until analysis. Before analysis, samples were thawed slowly and mixed gently.

VCAM-1, E-Selectin, VEGF, bFGF and vWF were measured in the serum, in duplicates, following the protocols provided by the manufacturer. [Human VCAM-1 ELISA kit (R&D Systems, Abingdon, UK), human E-Selectin ELISA kit (R&D Systems Ltd.; Oxford, UK), human VEGF ELISA kit (R&D systems, Abingdon, UK), human bFGF ELISA kit (R&D Systems, Abingdon, UK), human vWF ELISA kit (Alpha Labs, Hants, UK)]. We chose the above markers as surrogate markers of angiogenesis based on previous phase II trials evaluating these markers with other anti-angiogenic drugs conducted in our unit [25-27].

Statistical methods

At the time of the design of the study the effects of thalidomide in combination with carboplatin chemotherapy were not known, particularly effects on the levels of plasma/serum surrogate markers of angiogenesis. Therefore, there was no data in the literature on which number of patients required could be decided. Forty patients were chosen to evaluate if there would be any effect on circulating angiogenic markers based on previous phase II trials evaluating these markers with other anti-angiogenic drugs conducted in our unit [25-27]. In all these studies effects on surrogate markers were observed with a similar number of patients. To clearly delineate the effects of thalidomide, we felt it was preferable to do a randomised study rather than a simple phase II trial. This would separate any effects of carboplatin on the measurement of surrogate markers. The paired t-test was used to analyse differences in surrogate markers of angiogenesis before and after treatment in both groups and linear regression analysis was used to evaluate the differences between the two groups.

Results

Patient data

From 1998 to 2002, a total of 40 patients were enrolled into the trial (20 patients to the carboplatin-alone group and 20 to the carboplatin and thalidomide group). Patient characteristics are summarised in Table 1. Apart from four patients with adverse histological features like clear cell and mucinous who were randomised by chance to the carboplatin and thalidomide group, patient characteristics were similar in both treatment groups. Ninety-five percent of patients (19 out of 20) in the carboplatin group and 70% of patients in the carboplatin and thalidomide group (14 out of 20) received six cycles of treatment. Six patients in the experimental arm received less than the intended six cycles of treatment. One patient died after completing five cycles and one patient died after completing two cycles of treatment. Two patients had progressive disease after three cycles and two patients discontinued treatment after three cycles due to toxicity (peripheral sensory neuropathy in one patient and fatigue in another patient).

Table 1. — *Patient characteristics*.

Characteristics	Carboplatin	Carboplatin/ Thalidomide
No. of patients	20	20
Median age, years (range)	69.5 (41 to 84)	68 (40 to 80)
WHO Performance status		
0	11	8
1	7	9
2	2	3
3	0	0
Stage at time of diagnosis		
I- II	5	6
III-IV	15	14
Radical surgery		
(BSO ± TAH + Omentectomy)	12	13
Residual disease at the end of surgery		
< 2 cm	9	11
≥ 2 cm	11	9
Histology of the tumour		
Serous	11	7
Endometrioid	6	5
Mucinous	0	2
Clear cell	0	2
Primary peritoneal carcinoma	2	1
Adenocarcinoma	1	3
Grade of the tumour		
Well differentiated	0	1
Moderately differentiated	9	6
Poorly differentiated	11	9
Not known	0	4
No. of cycles of treatment received		
6	19	14
5	0	1
4	0	0
3	0	4
2	1	1

BSO, bilateral salpingo-oophrectomy; TAH, total abdominal hysterectomy.

Table 2. — *Incidence of treatment-related adverse events*.

	Carboplatin				Carboplatin/Thalidomide			
Grade	1	2	3	4	1	2	3	4
Anaemia	4	13	0	0	6	10	1	0
Leucopenia	6	3	0	0	6	5	1	0
Neutropenia	4	3	0	0	2	3	1	0
Thrombocytopenia	3	0	1	0	4	0	0	0
Nausea/Vomiting	5	8	3	0	4	8	1	1
Sensory neuropathy	3	0	0	0	4	1	1	0
Dizziness	1	0	0	0	0	1	0	0
Constipation	1	2	0	0	4	1	0	0
Tiredness	9	2	0	0	7	9	0	0

n = 20 patients. The figures represent number of patients.

Table 3A. — *Mean value for serum markers in the carboplatin arm*.

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
E-selectin (ng/ml)	31	28.8	23.2	26.2	24	23
bFGF (pg/ml)	15	6.7	5.5	7.9	3.9	5
VEGF (pg/ml)	713.5	232.9	273.7	449.5	360.6	246.6
Urine VEGF (ng/g creatinine)	919.2	182.8	121.8	168.8	145	146.2
VCAM-1 (ng/ml)	556.8	513.6	450.3	478.6	486.6	470.4
vWF (IU/dl)	136.9	127.4	134.6	129.7	131.5	133
CA-125 (IU/l)	417.4	400.4	223.9	183.2	164.4	141.5

n = 19 patients for all markers and at least 3 cycles of chemotherapy to have been completed.

Table 3B. — *Mean value for serum markers in the carboplatin/thalidomide arm*.

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
E-selectin (ng/ml)	49	41.5	39.7	38.1	37.5	38
bFGF (pg/ml)	14.5	10.8	4.2	4.4	3.9	5.9
VEGF (pg/ml)	671.3	369.4	295	376.7	403.9	429.2
Urine VEGF (ng/g creatinine)	415.7	227.5	219.3	208.6	130.4	135
VCAM-1 (ng/ml)	704.3	704.4	657.5	691.9	665.9	614.8
vWF (IU/dl)	139	148.5	143.1	142.2	132	129.5
CA-125 (IU/l)	1991.5	511.6	234.2	123.2	115.6	167.5

n = 17 patients for all markers and at least 3 cycles of chemotherapy to have been completed.

Toxicity

All patients who received any treatment were evaluated for toxic effects. The observed toxicities are summarised in Table 2. Haematological toxicities were mild in both treatment groups. Of the non-haematological toxicities, the most common adverse events in both treatment groups were grade 1-2 nausea, tiredness, constipation and dizziness. Three patients in the carboplatin group experienced grade 3 nausea and one patient in the combination group developed grade 4 nausea. More patients in the carboplatin and thalidomide group developed constipation (5 vs 3), tiredness (16 vs 11) and symptoms suggestive of peripheral neuropathy (6 vs 3), when compared with the carboplatin group. No major abnormality was detected in baseline and follow-up SNAP tests in either treatment group except for one patient in the carboplatin and thalidomide arm who developed transient grade 3 peripheral neuropathy and SNAP test showed a mild axonal polyneuropathy.

Fig. 1

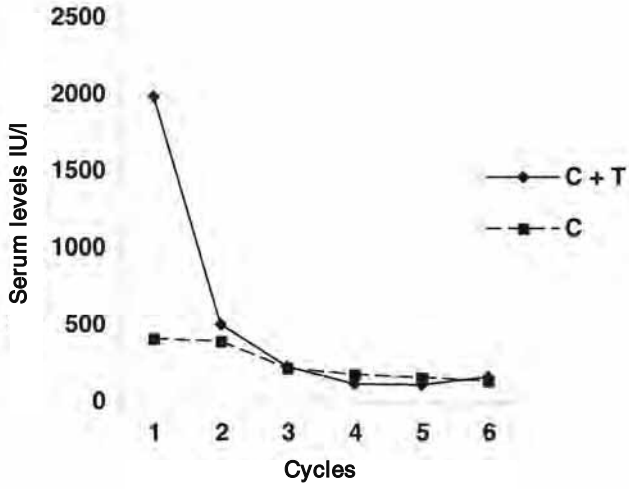

Fig. 2

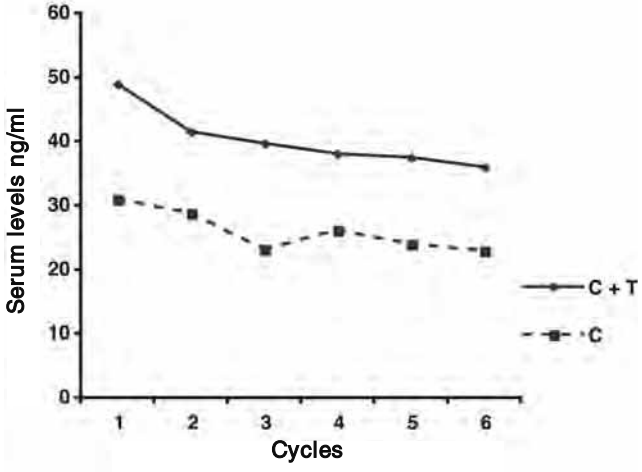

Figure 1. — *Serum CA-125 levels*.
Mean serum CA-125 lines of patients in both arms with each cycle of treatment. The fall was significant ($p < 0.001$) in both arms but not between groups.

Figure 2. — *Serum E-selectin levels*.
There was a significant fall in E-selectin in carboplatin ($p = 0.01$) and carboplatin/thalidomide ($p= 0.001$) groups after treatment. There was no significant change in the levels of E-Selectin between the two groups. C - Carboplatin (n = 19); C+T - carboplatin and thalidomide (n= 17).

Fig. 3

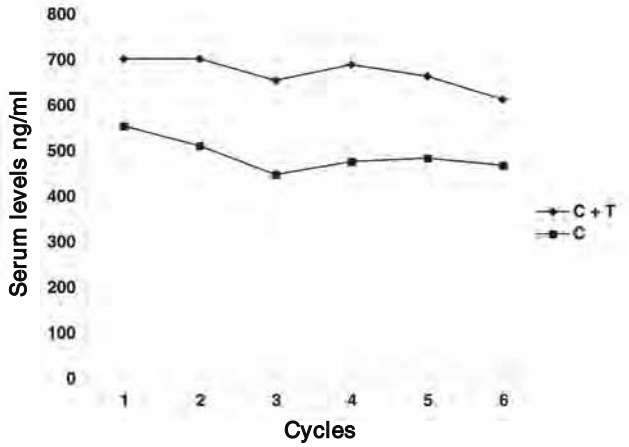

Figure 3. — *Serum VCAM-1 levels*.
There was a significant fall in VCAM-1 in carboplatin group ($p = 0.01$) but not in the carboplatin and thalidomide group ($p = 0.36$). There was no significant change in the levels of VCAM-1 between the two groups. C - carboplatin (n = 19); C+T - carboplatin and thalidomide (n = 17).

Response to therapy

Patients who received three or more cycles of chemotherapy with or without thalidomide were included for analysis of efficacy. Nineteen out of 20 patients in each group were evaluable for response. In the carboplatin group 11 patients achieved complete response (CR) and seven patients achieved partial response (PR) (overall response rate 90%). Disease stabilised in one patient and none of the patients developed progressive disease. In contrast, in the carboplatin and thalidomide group eight patients achieved CR, and PR was seen in seven patients, and one patient achieved disease stabilisation (overall response rate 75%). However, three patients in this group had progressive disease on treatment. There was statistically no significant difference in overall response rate (CR+PR) ($p = 0.41$) and complete response ($p = 0.34$) between the two treatment groups.

Surrogate markers of angiogenesis

The results for the serum surrogate markers of angiogenesis and serum CA-125 were evaluated in 19 patients in the carboplatin group (Table 3A) and 17 patients in the combination group (Table 3B). There were wide inter and intra-individual differences in surrogate markers of angiogenesis in both treatment groups. There was a significant fall in CA-125 and E-selectin in the carboplatin arm ($p < 0.001$ and $p = 0.01$) and in the carboplatin and thalidomide arm ($p < 0.001$ and $p = 0.001$) (Figures 1 and 2). The higher mean value of CA-125 at baseline and at the end of treatment in the combination group was due to very high values of CA-125 in a few patients in that group. VCAM-1 levels decreased significantly in the carboplatin group ($p = 0.01$) and a non-significant fall ($p = 0.36$) was observed in the combination group (Figure 3). There were no significant changes in the level of other markers in either treatment group. None of the analysed markers including CA-125 showed any significant difference between the two groups.

Discussion

Targeting tumour angiogenesis as an anti-cancer strategy is well established in solid tumours. In addition, a combination of standard chemotherapy with angiogenesis inhibitor may enhance therapeutic efficacy as such an

approach allows the use of agents with complimentary mechanisms of action and potentially non-overlapping toxicities. We evaluated the role of thalidomide in combination with carboplatin in a phase II randomised trial in ovarian cancer. We also investigated the anti-angiogenic effects of thalidomide.

We have shown that the combination of carboplatin and thalidomide is well tolerated in most patients. As expected, the incidence of constipation, tiredness, dizziness and peripheral neuropathy was more common in the thalidomide and carboplatin arm. When compared with the most recent trials that used thalidomide at a higher dose (400 – 600 mg/day) in combination with chemotherapy, the relative lack of toxicity we observed in our study is not surprising [24, 25]. No significant neurotoxicity was observed either clinically or as assessed by SNAP test and this observation was similar to other published studies [28, 29].

We could not demonstrate the expected increased efficacy by the addition of thalidomide to carboplatin in chemotherapy naïve ovarian cancer patients. There was no significant difference between the carboplatin and carboplatin/thalidomide groups in terms of disease response (90% vs 75%, $p = 0.41$). In contrast to our study, increased response rate to a combination of thalidomide (median dose of 200 mg/day) and topotecan has been demonstrated in a prospective trial, which compared the above combination with topotecan alone in women with recurrent ovarian cancer (47% vs 21% $p = 0.03$) [30]. The lack of additional therapeutic effect in our study may be due to a number of factors such as the relatively small size of patient groups or to the relatively lower dose of thalidomide used in this study. In addition, there were more patients with relatively chemo-resistant clear cell and mucinous tumours (20%) in the carboplatin and thalidomide group compared to the carboplatin group and six patients in the combination group did not complete the intended six cycles of treatment either due to disease progression or toxicity.

We also investigated surrogate markers of angiogenesis by serial blood sampling in patients. There was a significant decrease in CA-125 and serum E-selectin in both groups and VCAM-1 in the carboplatin group alone. None of the analysed markers showed significant differences between the groups. We propose that the reductions seen in levels of the above markers may suggest a tumour response to treatment rather than a specific anti-angiogenic action of thalidomide. In addition, it is possible that chemotherapy alone could have effects on the markers of angiogenesis. Similar to our study, no significant changes in the angiogenic markers like VEGF and bFGF were seen in prostate cancer patients treated with thalidomide [31]. However, this contrasts with studies reported in haematological disorders where significant reductions in the bone marrow microvessel densities and circulating levels of bFGF and VEGF had been observed in patients who responding to escalating doses of thalidomide (100 to 600 mg/day) [32, 33]. Our inability to demonstrate anti-angiogenic activity of thalidomide may be due to the dose and schedule of thalidomide used in our study and may also be related to the relatively small number of patients recruited into this study. Given the general lack of consensus among investigators with regards to optimal surrogate markers of angiogenesis to be used in clinical trials, it has recently been suggested that circulating endothelial precursor cells (CEPs), which are genetically predetermined and regulated by angiogenic factors may be a reliable marker [34]. In colorectal cancer patients treated with an anti-VEGF antibody, there was lowering of the levels of CEPs in whom the antibody was active in slowing tumour growth [35]. Thus measurement of CEPs in peripheral blood by flow cytometry may help in the future to optimise the dose of angiogenesis inhibitors and also to monitor their efficacy [36].

We conclude that the addition of thalidomide at the dose used in our study in combination with carboplatin as a first-line treatment in patients with ovarian cancer is safe and well tolerated. Failure to demonstrate increased efficacy of the above combination over carboplatin alone may be due to many factors as discussed above. Thalidomide and its analogues may have a role in recurrent ovarian cancer either alone or in combination with chemotherapy [17, 18, 30]. The GOG 198 trial explored the role of thalidomide in a completely different clinical scenario. Relapsed ovarian cancer patients with biochemical recurrence (rising CA-125) only with no evidence of macroscopic relapse are randomised to receive thalidomide (200 mg/day with gradual increment to maximum of 400 mg/day) or tamoxifen (40 mg/day) for the period of one year. After the interim analysis of 139 patients, the trial was closed as thalidomide did not reduce the recurrence rate relative to tamoxifen and it was more toxic [37]. We believe the role of thalidomide and its analogues in ovarian cancer is yet to be defined.

Acknowledgements

We are grateful to patients who kindly participated in the study. Cancer Research UK supported the study. We acknowledge the support of the Department of Neurophysiology for SNAP tests. We thank Pamela White for her support in preparing the manuscript.

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