Original article

A phase II randomised, placebo-controlled trial of low dose (metronomic) cyclophosphamide and nintedanib (BIBF1120) in advanced ovarian, fallopian tube or primary peritoneal cancer

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Abstract

Background: We investigated the safety and efficacy of a combination of the oral tyrosine kinase inhibitor, nintedanib (BIBF 1120) with oral cyclophosphamide in patients with relapsed ovarian cancer.

Patients and Methods: Patients with relapsed ovarian, fallopian tube or primary peritoneal cancer received oral cyclophosphamide (100mg o.d.) and were randomised (1:1) to also have either oral nintedanib or placebo. The primary endpoint was overall survival (OS). Secondary endpoints included progression free survival (PFS), response rate, toxicity, and quality of life.

Results: 117 patients were randomised, 3 did not start trial treatment, median age 64 years. Forty-five (39%) had received ≥5 lines chemotherapy. 30% had received prior bevacizumab. The median OS was 6.8 (nintedanib) versus 6.4 (placebo) months (hazard ratio 1.08; 95% confidence interval 0.72-1.62; *P* = 0.72). The 6-month PFS rate was 29.6% versus 22.8% (*P*=0.57). Grade 3/4 adverse events occurred in 64% (nintedanib) versus 54% (placebo) of patients (*P*=0.28); the most frequent G3/4 toxicities were lymphopenia (18.6% nintedanib versus 16.4% placebo), diarrhoea (13.6% versus 0%), neutropenia (11.9% versus 0%), fatigue (10.2% versus 9.1%), and vomiting (10.2% versus 7.3%). Patients who had received prior bevacizumab treatment had 52 days less time on treatment (*P*<0.01). 26 patients (23%) took oral cyclophosphamide for ≥6 months. There were no differences in quality of life between treatment arms.

Conclusions: This is the largest reported cohort of patients with relapsed ovarian cancer treated with oral cyclophosphamide. Nintedanib did not improve outcomes when added to oral cyclophosphamide. Although not significant, more patients than

expected remained on treatment for ≥6 months. This may reflect a higher proportion of patients with more indolent disease or the higher dose of cyclophosphamide used.

Clinical Trial Registration: Clinicaltrials.gov NCT01610869

Key words: late stage relapsed ovarian cancer, oral cyclophosphamide, nintedanib, prior bevacizumab

Key Message/ Highlights:

- Nintedanib added to oral cyclophosphamide did not improve outcome in heavily treated patients with relapsed ovarian cancer
- 36% of patients derived clinical benefit from cyclophosphamide (10% PR/CR and 26% SD); 23% continued treatment at 6 months
- Oral cyclophosphamide 100mg daily is tolerable; adverse events were mostly related to the companion antiangiogenic agent.
- Prolonged disease stabilisation was seen in 11 patients.

Introduction/ Background

Ovarian carcinoma (OC), encompassing fallopian tube and primary peritoneal cancers, is the most common cause of gynaecological cancer death in the Western world[1]. Patients with relapsed OC are very unlikely to be cured and should be considered to have a chronic disease which will relapse and remit. Sequential treatment strategies are employed to maximise quality and length of life, but ovarian cancer will eventually become resistant to standard treatments. Non-toxic therapies that are simple to administer are sought for patients at this stage. Alkylating agents are not considered a routine option in the current management, but the efficacy of agents such as cyclophosphamide and chlorambucil in OC is established and their use predates that of platinum-based drugs.

Angiogenesis has been shown to have a significant role in ovarian cancer. Bevacizumab, a humanised monoclonal antibody targeting vascular endothelial growth factor (VEGF), is approved for use in combination with and as maintenance following chemotherapy in OC patients. Evidence supporting the use of bevacizumab or the VEGFR inhibitor pazopanib with weekly paclitaxel in platinum resistant relapsed OC is particularly compelling with a doubling of progression-free survival[2,3]. The combination of bevacizumab and continuous metronomic oral cyclophosphamide (doses lower than the maximum tolerated dose) has also been shown, in a number of retrospective and single-arm studies, to have good therapeutic activity in relapsed OC[4,5,6].

Cyclophosphamide is an alkylating agent; when given orally at metronomic doses it is thought to have additional antiangiogenic properties, for example it has been shown to have increased activity against endothelial cells, which, although derived from the host stroma, generally proliferate rapidly in tumours[7]. Metronomic chemotherapy is treatment given at lower than maximum tolerated doses and at short regular intervals eg. daily, with no prolonged breaks. Such scheduling is thought to target angiogenesis by obliterating proliferating endothelial cells and circulating endothelial cell precursors. Additionally, metronomic cyclophosphamide has been shown in breast cancer to reduce levels of serum VEGF, a key regulator of the process of angiogenesis[8].

Several tyrosine kinase inhibitors exhibit antiangiogenic effects and have demonstrated activity in recurrent OC [9,10,11]. Nintedanib is a potent, orally available triple kinase inhibitor targeting VEGF receptors, platelet-derived and fibroblast growth factor receptors (PDGFR/FGFR). The specific and simultaneous abrogation of these pathways results in effective growth inhibition of both endothelial and, via PDGFR and

FGFR, perivascular cells, which may be more effective than inhibition of endothelial cell growth via the VEGF pathway alone. Signalling by FGFR has also been identified as a possible escape mechanism for tumour angiogenesis when the VEGF pathway is disrupted.

Although there are no specific preclinical studies of nintedanib with cyclophosphamide, numerous preclinical and clinical studies support the assumption that VEGF and PDGF are key targets for the management of OC. The combination of antiangiogenics, such as bevacizumab or pazopanib with continuous metronomic oral cyclophosphamide have been shown to have good therapeutic activity in relapsed OC[4,5,6].

Here we sought to determine the tolerability and efficacy of a combination of oral metronomic cyclophosphamide (OMC) with the anti-angiogenic nintedanib in heavily pre-treated, relapsed OC patients. A dose of 100mg daily was chosen to explore the value of a tolerable, maximal metronomic dose. Early studies of metronomic cyclophosphamide have described outcomes from using a dose to maintain white blood cell count $\geq 1.5 \times 10^9$/l ; the most common daily dose in 54 patients was identified as 100-150mg daily[12]. Acceptability of this dose was confirmed in other reports[13-15]; in vitro studies of metronomic cyclophosphamide are generally 2-20 mg/kg (~140-1400 mg for 70kg person)[16,17]. Finally, in breast cancer, classical CMF adjuvant chemotherapy requires a dose of 80mg/m^2, thus patients of standard height / weight (BSA = 1.7 / 1.8m^2), receive~130mg daily[18]. Handiolas et al have reported 44% response rate to OMC given as per CMF (50-150mg/day for the first 14 of every 28 days) in heavily pretreated ovarian cancer patients[19].

Materials / Methods [534]

Study population and eligibility criteria

Patients >18 years with histological confirmation of ovarian, fallopian tube or primary peritoneal carcinoma, who had received ≥ 2 lines of prior chemotherapy and were considered to be platinum resistant or intolerant or unsuitable for further intravenous chemotherapy were enrolled. Patients could have had a non-platinum agent as last prior treatment as long as they had relapsed within 6 months of their last platinum and within 6 months of completing their last chemotherapy. Use of prior bevacizumab was permitted but prior cyclophosphamide or tyrosine kinase inhibitor treatments were not. See supplementary data for full inclusion/exclusion criteria.

Randomisation and Treatment Schedule

We conducted a double-blind randomised controlled phase II trial. Patients were randomly allocated (1:1) to receive oral nintedanib or matching placebo continuously until disease progression death or adverse events. Randomisation was performed using an interactive web-based system, with stratified randomisation according to: age (≤60 and >60), previous lines of chemotherapy (≤3 or >3) and previous bevacizumab treatment (yes or no).

All patients were given OMC (100mg once daily), in cycles of 6 weeks. When the trial began, the starting dose of nintedanib was 200mg twice daily. The Independent Data Monitoring Committee examined SAEs and toxicity data from the initial 61 patients. As a result, a reduced starting dose of nintedanib/placebo to 150mg b.d was implemented for future recruits. Dose reductions were allowed to a minimum of 100mg b.d. nintedanib/placebo and 50mg o.d. OMC. See supplementary data, for full modification schedule.

Assessments

All patients had computed tomography (CT) of abdomen, pelvis and / or MRI with high resolution CT imaging of the chest at baseline. Imaging was repeated every 12 weeks. Patients were not required to have RECIST measurable disease for trial entry. Haematology, biochemistry and toxicity were assessed every three weeks for the first 6 weeks then every 6 weeks. The first 12 patients (run-in safety cohort) were reviewed every 3 weeks for 12 weeks. CA125 was measured at baseline then every 6 weeks. Adverse events were categorised using NCI CTCAE v 4.1. Quality of life (QoL) was assessed using EORTC QLQ-C30, OV28 and MOST Recent Symptoms questionnaires[20].

Statistical considerations

The primary endpoint was overall survival (OS). A retrospective audit of patients treated with OMC indicated a median OS of 5 months[13]. We aimed to detect an increase of 2 months using nintedanib, i.e. a median OS of 7 months (equivalent to a hazard ratio (HR) of 0.71), consistent with the PFS reported for combination bevacizumab/OMC[5]. With 80% power and one-sided 20% significance level, 56 patients per group were required (assuming 18 months of recruitment and 12 months of follow-up); i.e. 112 patients in total (or 100 deaths). With 10% allowance for non-compliance, recruitment of 124 patients was planned. Secondary efficacy endpoints included progression-free survival (PFS), 6-month progression-free survival and response rate. Both endpoints were based on RECIST 1.1 and GCIG CA125 criteria. OS and PFS were examined using Kaplan-Meier plots and Cox regression. Response rates were assessed where data were available. Adverse events were compared using the maximum grade for each patient and each event type. QoL was compared

using repeated measures modelling. The safety population was defined as all patients who took at least one dose of OMC and nintedanib/placebo.

Results

Patient demographics

A total of 117 patients were randomised (N=59 nintedanib, N=58 placebo) from 11 sites between August 2014 and October 2016 (Figure 1 CONSORT diagram). 3 patients in the placebo group did not start trial treatment. 59 and 55 patients received at least one dose of nintedanib or placebo respectively and form the safety population. Baseline/clinical characteristics are shown in Table 1. Median age was 64 years. The median number of prior lines of chemotherapy was 4, with 38% (43 patients) having received 3 lines or less, and 39% (45 patients) having received 5 lines or more. Most patients had high grade serous tumours (87%). 31% patients had previously received bevacizumab.

Treatment duration

Overall 85 (73%) of the 117 randomised patients completed 6 weeks (1 cycle) of treatment. 29 patients who started the treatment (25%) stopped trial therapy prior to this and 3 patients in the placebo group failed to start any study treatment. 26 patients (23%) continued with OMC for more than 6 months (Figure 3 and Appendix Figure 2), with eight (7%) patients continuing treatment for more than 11 months. One patient was lost to follow-up after their week 6 visit. Overall treatment was stopped for the following reasons: disease progression (68%), AEs (16%), withdrawal of consent (5%), non-compliance (1%) and other reasons (11%).

Efficacy

Median follow-up time was 1.6 years (interquartile range (IQR) 1.4–1.9 years). No difference in OS: the median was 6.8 months for nintedanib and 6.4 months for placebo (Figure 2A). The hazard ratio (HR) for nintedanib versus placebo was 1.03 (95%CI 0.69-1.55; p-value 0.87). However, 20.4% and 31.3% patients in the nintedanib and placebo groups respectively were still alive at 12 months.

Median PFS was 2.9 months for nintedanib and 2.6 months for placebo (Figure 2B). 6 month PFS rates were 29.6% and 22.9% for nintedanib/placebo respectively, HR 0.91 (95%CI 0.62-1.32; p-value 0.61).

Radiological RECIST (version 1.1) responses were seen in 11/114 (9.6%) patients, 1 complete response (CR),4 partial responses (PR) in the nintedanib group and 1 CR, 5 PR in the placebo group. 26.3% (30/114) of patients (17 nintedanib, 13 placebo) had RECIST defined stable disease ie. no CR, PR or PD on the subsequent three-monthly scan. Two patients, without RECIST evaluable disease, did not progress by CA125 GCIG criteria. 57/114 (50%) progressed on trial treatment according to RECIST, 4 patients (3.5%) progressed according to CA125 GCIG criteria alone (Appendix Table 1).

Hypothesis generating subgroup analyses were performed using the stratification factors outlined in Table 2. A statistically significant interaction with the treatment was found for PFS according to the number of previous lines of chemotherapy. The HR for patients with $\leq$3 lines was 0.53 (95% CI 0.28-0.99) compared to 1.19 (95% CI 0.74-1.92) for patients with >3 lines (interaction p=0.04). In the subgroup who had $\leq$3 lines (n=43), the HR remained statistically significant after adjustment for age and previous VEGF inhibitor treatment (adjusted HR=0.47, 95% CI 0.24-0.91; p=0.03) (Appendix Fig 1).

Median time on OMC was 82 days (IQR 43-155, mean 112) with a minimum of 3 days and a maximum of 610 days (Fig 3). The population who had received prior bevacizumab had shorter durations of treatment with OMC irrespective of randomisation to nintedanib or placebo, by a mean of 52 days ($p < 0.01$; Appendix Figure 3).

Quality of life

111 patients completed QoL questionnaires at baseline, 80 patients at both baseline and after 1 cycle of treatment (Appendix Tables 2 to 4). Scores were slightly higher in the nintedanib versus placebo group for “hormonal/menopausal symptoms” and “other chemotherapy side-effects” on the symptom scales of QLQ-OV28. There was no effect of nintedanib on any of the functional scales of QLQ-C30 Global Health state or QLQ-OV28 between baseline and week 6. Equally there was no effect of nintedanib on any the five scales of the MOST questionnaire.

Adverse events

Many adverse events (AEs) represented symptoms commonly experienced by patients with relapsed OC, a significant proportion occurring within the first 6 weeks. Some AEs matched recognised side effects of nintedanib treatment. There was insufficient toxicity to recommend halting recruitment after the first 12 patients, however the IDMC examined the SAEs and toxicity data after 61 patients. They found it difficult to determine the exact aetiology of the range of AEs reported in this larger cohort but evaluating the spectrum of toxicity recommended reducing the dose of nintedanib to 150mg b.d. for the remainder of the study. However, many of the 61

patients, recruited prior to the IDMC review, did tolerate the higher 200mg b.d. dose; they were allowed to continue at this dose, at the discretion of the treating investigator. All grades of AE, according to NCI CTCAE v 4.1 criteria, are summarised in Appendix Table 5. All patients except one (in the placebo group) experienced at least one event of any grade. Grade 3/4 AEs (Table 3) occurred in 64% (38/59) nintedanib versus 54% (30/55) placebo. Some of these represented worsening of pre-existing symptoms, already been present at baseline, i.e. grade 1/2 events at randomisation becoming grade 3/4 after starting the trial treatments. The most frequent grade 3/4 toxicities were lymphopenia (20.3% vs.18.2%, nintedanib/placebo), diarrhoea (15.3% vs. 0%), neutropenia (11.9% vs. 0%), fatigue (11.9% vs. 9.1%), and vomiting (10.2% vs. 7.3%). Grade 1/2 toxicities occurred in 59/59 (100%) nintedanib versus 52/55 (94%) placebo, with the most frequent being nausea (78.0% v 50.9%), vomiting (54.2% v 47.3%) and diarrhoea (47.5% v 45.5%). After the dose of nintedanib was reduced to 150mg b.d., the incidence of toxicities was similar between the trial groups: grade 3/4 events 63% (17/27) nintedanib versus 67% (18/27) placebo, with corresponding grade 1/2 events for 100% (27/27) and 93% (25/27).

Discussion.

Cyclophosphamide has been somewhat neglected since trials showed the superiority of carboplatin/paclitaxel over cisplatin/cyclophosphamide[21]. Yet in this trial, the largest reported group treated with OMC to date, we show that OMC is tolerable in patients with relapsed OC, despite numerous prior lines of therapy (39% had ≥5 lines). Indeed the 6-month PFS rates of 29.6% and 22.9% for nintedanib/placebo respectively are similar to those seen in a less heavily treated population (all ≤3 lines) who had weekly paclitaxel alone[22].

A slightly higher dose of OMC, 100mg daily, was used in our trial in contrast to many other studies where 50mg per day has been used [4-6, 23]. As previously described, this higher dose was well tolerated with grade 3/4 toxicity limited to lymphopenia, fatigue and abdominal pain in the control arm[12-15,18,19]. Endorsement of the decision by the IDMC to reduce the nintedanib dose is evident from the equivalent incidence of toxicity in both arms for subsequently recruited patients (grade 3/4 events 63% nintedanib versus 67% placebo, grade 1/2 events in 100% versus 93%). There was a 10% higher overall incidence of toxicity seen in those treated with combination versus OMC alone with the inclusion of the population treated prior to the IDMC decision (Table 3). Despite this, overall 75% of the population completed 6 weeks of treatment and 23% stayed on therapy for longer than 6 months.

Since our trial was designed, several other studies have explored the combination of OMC with antiangiogenics in recurrent ovarian cancer. Barber et al report a 42% response rate in heavily pretreated (median 6.5 prior lines) relapsed OC patients receiving bevacizumab and OMC[24]. Dinkic et al reported a median PFS and OS of 8.5 and 25 months respectively in a 16-patient Phase I dose-finding study of relapsed OC

patients (median 2 prior lines) combining OMC and pazopanib[25]. Again the anti-angiogenic component caused the most significant adverse events, leading to dose limitation at 600mg for pazopanib.

Our trial is the first to explore the potential for nintedanib therapy in very heavily pretreated (median of 4 prior lines, 39% ≥ 5 lines) patients with recurrent OC. The significantly longer PFS for nintedanib patients who had had < 3 prior lines of chemotherapy corroborates other evidence that better outcomes are seen for antiangiogenic therapies in less heavily pretreated patients[2,3]. Taken as a whole, cyclophosphamide-treated patients who had *not* received bevacizumab had a longer duration of therapy (Appendix Figure 3). This may simply reflect the poorer overall prognosis of those treated with bevacizumab in the UK.

However, the successful mechanisms of action of OMC may not be entirely antiangiogenic. OMC has been shown to deplete T regulatory cells and restore effector functions of T cells and natural killer cells [26,27]. Additionally, modulation of the abnormal tumour vasculature by OMC may enhance an immune-supportive tumour microenvironment eg. allowing accumulation of effector T cells, leading to prolonged responses/disease stabilisation in small groups of patients[28,29]. (Appendix Figure 3.) This concept should be explored further.

A limitation of our trial is the lack of *BRCA* status because routine *BRCA* testing was not available during recruitment to METRO-BIBF. However, Kummar et al. report no benefit in adding the PARP inhibitor, veliparib, to OMC in the treatment of 72 relapsed OC patients, despite 43% of this population having a known *BRCA* mutation (60% *BRCA* unknown). They explored the association of *BRCA*, and other DNA repair defects, with response to OMC and found no clear relationship[30].

In summary, amongst a very heavily pretreated population of relapsed OC patients, nintedanib did not improve clinical outcomes when combined with OMC. However, we note that 36% of patients derived clinical benefit (10% PR/CR and 26% SD). In the context of platinum resistant relapsed OC where women have received a median of 4 prior lines, the fact that 23% remained on treatment at 6 months is an indicator of clinical benefit. Additionally, in this setting, where practical issues such as the number of impending hospital visits and poor venous access become increasingly important to maintain quality of life, OMC with 6 weekly monitoring could be considered an appropriate therapeutic option.

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