Combined Oral Topotecan plus Carboplatin in Relapsed or Advanced Cervical Cancer: A GINECO Phase I-II Trial

J.E. KURTZ[1], G. FREYER[2], F. JOLY[3], L. GLADIEFF[4], M.C. KAMINSKI[5], M. FABBRO[6], A. FLOQUET[7], A.C. HARDY-BESSARD[8], N. RABAN[9], I. RAY-COQUARD[10] and E. PUJADE-LAURAINE[11]; ON BEHALF OF THE GINECO GROUP, FRANCE

[1]*Oncology and Haematology Department, Hautepierre Hospital, Strasbourg, France;*
[2]*Oncology Department, Lyon Sud Hospital, Pierre-Bénite, France;*
[3]*Oncology Department, François Baclesse Anticancer Center, Caen, France;*
[4]*Oncology Department, Claudius Regaud Institute, Toulouse, France;*
[5]*Medicine Department, Alexis Vautrin Anticancer Center, Vandœuvre-lès-Nancy, France;*
[6]*Oncology Department, Val d'Aurelle Anticancer Center, Montpellier, Farnce;*
[7]*Oncology Department, Bergonié Institute, Bordeaux, France;*
[8]*Armorican Radiology Clinic, Saint Brieuc, France;*
[9]*Oncology Department, Poitiers University Hospital, Poitiers, France;*
[10]*Oncology Department, Léon Bérard Anticancer Center, Lyon, France;*
[11]*Oncology Department, Hôtel-Dieu Hospital-University Paris Descartes, Paris, France*

Abstract. *Aim: Combined cisplatin-topotecan therapy is standard care for advanced cervical cancer, however it is associated with haematotoxicity and nephrotoxicity. This trial was designed to assess the combination of carboplatin which is less nephrotoxic, and oral topotecan. Patients and Methods: Patients with advanced/recurrent squamous cervical cancer received carboplatin (AUC5) on day 1, with escalating oral topotecan (3.0 mg/m^2 starting dose) on days 1, 8 and 15, every 4 weeks. Endpoints were the maximal tolerated dose for the phase I part and safety profiles and response rates for the phase II part of the study. Results: Two dose levels were evaluated. A total of 18 patients (6 phase I, 12 phase II) were treated. The maximal tolerated dose was 3.0 mg/m^2 topotecan with carboplatin AUC5. Phase II accrual was interrupted following unacceptable toxicity, with 10 therapy-related related serious events in 9 out of 12 patients: grade 3-4 pancytopenia (7), febrile neutropenia (1), grade 3 haemorrhage (1) and grade 3 vomiting (1). Conclusion: Weekly oral topotecan combined with carboplatin is associated with unmanageable toxicity and is not recommended. Future studies are warranted to better understand the toxicity of such a combination and explore alternative combinations for advanced cervical cancer.*

Correspondence to: Prof. Jean-Emmanuel Kurtz, Oncology and Haematology Department, Hautepierre Hospital, 1 Av Molière, 67098 Strasbourg, France. Tel: +33 388128314, Fax: +33 388127681, e-mail: j-emmanuel.kurtz@chru-strasbourg.fr

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Cervical cancer ranks second in prevalence among cancers affecting females worldwide, accounting for 250,000 deaths per year. With the introduction of screening programs in developed countries, the incidence of cervical cancer is constantly decreasing, a trend which will be reinforced by the widespread implementation of human papillomavirus vaccination programs. While localized cervical cancer can be cured by surgery and or combined modality treatment, prognosis of advanced disease remains dismal, with 5-year survival for FIGO stage IV patients of between 5% and 15% (1).

Topotecan is a specific topoisomerase I inhibitor which forms a stable complex with its target, and causes single-strand breaks in DNA. The weekly topotecan schedule is now well established and has proven to be both safe and effective, at least for ovarian cancer, with equivalent pharmacokinetics to other regimens (2, 3). In platinum-resistant ovarian cancer, the weekly schedule showed a slightly non-statistically shorter progression-free survival (PFS) than the conventional 5-day (1.25 mg/m^2/day) protocol, despite comparable overall survival (OS) and a better toxicity profile (4). Similar results were reported in another recent randomized phase II study in patients with platinum-sensitive disease, with the weekly schedule being less active but showing improved tolerance (5).

Single-agent topotecan, 1.5 mg/m^2 administered on days 1-5 every 4 weeks, is active against cervical cancer, with reported response rates of 12% to 18% (6), albeit with reported rates of 68% grade 4 neutropenia and 18% thrombocytopenia in the Gynecologic Oncology Group (GOG) 76-U phase II study (7). The activity of cisplatin, a standard therapy in the treatment of advanced cervical cancer, is potentiated when administered in combination with topotecan, via the inhibition of DNA repair (8). A phase II study evaluating combined cisplatin and topotecan for cervical cancer gave a 28% response rate (9). The same combination schedule (cisplatin 50 mg/m^2, day 1; topotecan 0.75 mg/m^2, days 1-3 every 3 weeks) was used in the GOG179 phase III trial in comparison with single-agent cisplatin (10). This landmark study established the combination as the standard for advanced cervical cancer, with a superior overall response rate (27% *versus* 13%), as well as improved PFS (4.6 *versus* 2.9 months) and OS (9.4 *versus* 6.5 months). However, the safety profile of the cisplatin-based doublet was characterized by increased haematological toxicity, with 70% *versus* 1.4% of patients experiencing grade 3-4 neutropenia in the combination and single-agent arms, respectively. Infection was consequently also more frequent, following the combination. This was, nonetheless, not associated with an impact on quality of life (11).

Peripheral neuropathy and renal toxicity associated with cisplatin therapy are serious drawbacks to its use. It is particularly important for one to take renal toxicity into consideration when combining cisplatin with topotecan, given the fact that the latter drug is eliminated by the kidneys after hydrolysis of its lactonic ring, potentially increasing topotecan-induced myelotoxicity (2).

Carboplatin is a well-known platinum salt which differs from cisplatin by its spectrum of toxicity, lacking both renal toxicity and peripheral neurotoxicity. Moreover, carboplatin has the additional advantage that dosing can be adapted to renal function using the area under the curve (AUC) method. Single-agent carboplatin has been shown to be active in cervical cancer; efficacy is comparable to the one of cisplatin, with response rates from 15 to 28% (12, 13), although it does have a greater marked myelotoxicity than cisplatin, particularly thrombocytopenia. A recent phase I/II combination of intravenous topotecan 2.5 mg/m^2 administered on days 1 and 8 with carboplatin AUC5 as second-line therapy for patients with platinum-sensitive disease showed an acceptable benefit/risk ratio, despite significant grade 3-4 neutropenia (14).

An oral formulation of topotecan has been developed and was approved for the treatment of non-small cell lung cancer in 2007 (15). Oral topotecan is rapidly absorbed and has 80% bioavailability. Dose adjustments are not required in patients with moderate renal insufficiency and its pharmacokinetic parameters are not influenced by concomitant cisplatin administration (16). As an approach to reduce nephrotoxicity of the cisplatin-based doublet for therapy of patients with advanced cervical cancer, we conducted a phase I-II dose escalation study, replacing cisplatin with carboplatin AUC5 in combination with oral topotecan.

Patients and Methods

Patient selection. To be eligible for the study, patients had to be at least 18 years old; have histologically proven squamous cell carcinoma or adenocarcinoma of the cervix, be in first relapse with locoregional invasion not amenable to surgery or radiochemotherapy, or have distant metastasis; have at least one measurable target lesion outside a prior radiation field; prior radiochemotherapy with platinum salts was permitted with a wash-out interval ≥6 months; performance status (ECOG) ≤2; ≥1.5×10^9/l neutrophils, ≥100×10^9/l platelets, ≤1.5 × the upper limit of normal (ULN) total bilirubin, ≤3 × ULN liver transaminases or ≤5 × ULN for those with liver metastases, creatinine clearance (Cockroft) ≥50 ml/min. Patients were excluded if they had received prior chemotherapy (except concomitant chemoradiation); brain metastasis; any other malignancy in the previous five years (except cured basocellular or spinocellular cancer); contraindications to study drugs; an inability to swallow; altered intestinal absorption, or a gastric/duodenal ulcer; nephrostomy; uncontrolled hypertension; class III-IV NYHA cardiac failure, angina pectoris, arrhythmia, or myocardial infarction within 6 months; were pregnant or breastfeeding. All patients provided written informed consent and the local Ethics Committee approval was obtained.

Study design and assessments. In the multicentre, phase I dose-finding part of the study, dose-limiting toxicities (DLTs) were defined as grade 4 leucopenia, neutropenia, or thrombocytopenia or any grade ≥3 non-haematological toxicity, except grade 3 alopecia or vomiting. Unresolved haematological toxicity at day 43 was also considered a DLT. Three patients were initially treated at each dose level. Dose escalation could be implemented after all three patients had received a complete treatment cycle with a four-week observation period. If one patient developed DLT, up to three additional patients were treated at the same dose level. If two or more patients at a given dose level had DLT, escalation was stopped and the previous level was considered the maximal tolerated dose (MTD). The MTD was then evaluated as the recommended dose in a phase II part of the study using a two-stage Simon optimal design. For a confirmed objective response rate of at least 25% (considered clinically promising) *versus* a maximum of 10% (considered not clinically promising), and with 80% power to detect a 25% response rate with a 0.05 level of significance, 43 patients were required. If no more than one of the first 18 evaluable patients responded, the study regimen was considered as not promising and accrual was to be stopped. If at least two patients responded, an additional 25 evaluable patients were to be accrued.

The starting dose of topotecan was 3.0 mg/m^2, and two higher dose levels were planned (3.7, 4.5 mg/m^2) and a lower dose (2.7 mg/m^2) was possible. Oral topotecan was administered weekly on days 1, 8 and 15, every 3 weeks in combination with a fixed dose of intravenous carboplatin AUC5 on day 1, every 3 weeks. Premedication included intravenous administration of setrons with or without steroids on day 1 and oral anti-emetics on days 8 and 15. Primary leucopenia/neutropenia prophylaxis was not recommended. Secondary prophylaxis (lenograstim) was mandatory if grade 3-4 neutropenia or

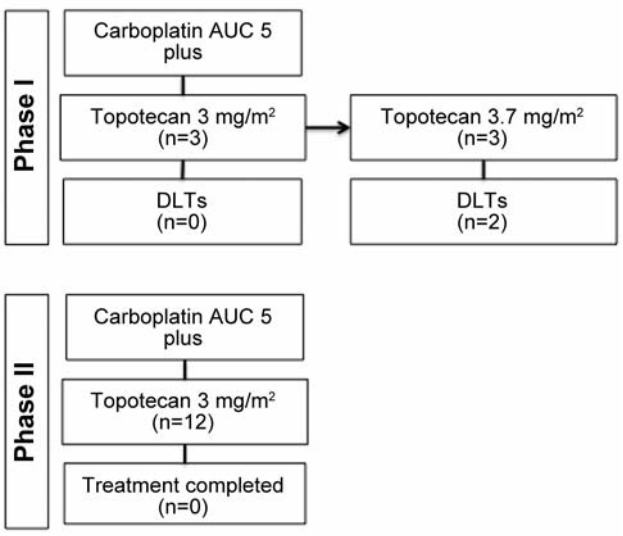

Figure 1. *Phase I-II study design, patient inclusion, doses and DLTs.*

febrile neutropenia occurred. Carboplatin was reduced to AUC4 in the event of febrile neutropenia or severe sepsis, unresolved grade 3 thrombocytopenia at day 36 or grade 4 thrombocytopenia. Topotecan was withdrawn following grade 3-4 leucopenia/ neutropenia on day 8 or 15, or persistent grade 2-4 thrombocytopenia. Haematological toxicity had to resolve to grade ≤1 prior to further treatment. Treatment was administered until progression or unacceptable toxicity, for a maximum of six cycles. Adverse events were assessed continuously and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3. Blood counts and creatinine clearance were evaluated weekly and liver biochemistry every four weeks. Tumour response was assessed every 12 weeks according to RECIST (version 1.0).

Table I. *Patients' characteristics.*

	Phase I (n=6)	Phase II (n=12)
Age, years, median (range)	51 (37-63)	47 (41-66)
Performance status (ECOG)		
0/1/2	2/4/-	5/6 /1
Histology		
Squamous cell	6	11
Adenocarcinoma	-	1
Grade		
Well differentiated	2	6
Intermediate	3	5
Undifferentiated	1	1
FIGO stage at diagnosis		
Ib	-	2
IIa/IIb	1/3	2/4
IIIa/IIIb	1/-	1/2
IVa/IVb	1/-	-/1
Prior treatment		
Surgery	6	10
Brachytherapy	5	9
External beam pelvic radiation therapy	5	10
Chemotherapy	5	9
Cisplatin	4	8
Carboplatin/paclitaxel	1	-
Platinum-based	-	1
Chemotherapy-free interval in months (n=14)		
Median (range)	16.7 (4.9-89.1)	9.2 (5.4-43.3)
Number of metastatic sites		
1/2/3/>3	-/3/2/1	2/4/3/3
Urinary/digestive tract history (n=8)		
Double J probe	2	4
Nephrostomy	1	-
Ileostomy	1	-
Colostomy	-	2

Results

Part I of the study. Six patients were treated in the phase I part of the trial, three at dose level 1 (3.0 mg/m^2 topotecan) and three at dose level 2 (3.7 mg/m^2; Figure 1). Patients' characteristics are shown in Table I. A total of 22 cycles were administered (median 3, range 3-6). No DLT was reported in the three patients treated at dose level 1. Two out of the three patients treated at dose level 2 had DLT (one with grade 4 neutropenia plus grade 3 thrombocytopenia; one with grade 3 neutropenia and thrombocytopenia), resulting in cancellation of day 15 topotecan administration for both patients.

Haematological toxicity was frequent in the six patients treated during the phase I part of the study, and was often severe, with grade 3-4 neutropenia in four patients, grade 3-4 thrombocytopenia in three patients and grade 3-4 anaemia in two patients. When it occurred, severe toxicity was most commonly reported during the first cycle. It was often severe: one patient had grade 4 neutropenia, grade 3 thrombopenia and grade 3 anemia; two patients had grade 3 neutropenia and grade 3 thrombopenia; one patient had grade 3 neutropenia; one patient had grade 3 anemia.

Dose reduction was implemented for two patients (one due to neutropenia and one due to febrile neutropenia). Treatment delay lasting at least seven days occurred in three (19%) chemotherapy cycles due to neutropenia (two patients). Grade 3-4 non-haematological toxicities occurred in two patients (one had pain and one had anorexia, both considered to be caused by the underlying disease). Five out of the six patients progressed after three or four cycles of chemotherapy (four and one patient, respectively). Given the fact that DLT occurred in two patients treated at 3.7 mg/m^2, the dose level below, 3.0 mg/m^2 topotecan/AUC5 carboplatin regimen (without DLT), was selected as the recommended dose for the phase II part of the trial. A partial response was obtained in one patient at dose level 2 who completed all six planned cycles.

Part II of the study. Twelve patients were enrolled in the phase II part of the study (Table I), receiving a total of 31 cycles of treatment (median 3, range 1-4) at 3.0 mg/m^2 topotecan/AUC5 carboplatin. Haematological toxicity was also common in these 12 patients, with grade 3-4 neutropenia in 10 patients (83%), grade 3-4 thrombocytopenia and leucopenia in 9 patients (75%) each, and grade 3-4 anaemia in 4 patients (33%). Furthermore, seven of the patients (58%) stopped treatment as a result of toxicity; five (42%) due to haematological toxicity, one (8%) due to renal failure and one (8%) due to fistula. Four patients (33%) progressed and one withdrew consent. Overall, 12 serious events were reported in nine out of the 12 patients. Ten of these events occurring in nine patients, were considered to be related; grade 3-4 pancytopenia (7 events), febrile neutropenia (1), grade 3 haemorrhage (1) and grade 3 vomiting (1). Seven related events occurred during the first two cycles, two in cycle 3, and one in cycle 4. One patient underwent dose reduction for nausea and vomiting and nine (29%) cycles were interrupted due to myelotoxicity. Treatment delays of at least seven days occurred in three (16%) chemotherapy cycles, all of which were due to neutropenia. Three phase II patients (25%) had a partial response and five additional patients (42%) had stable disease.

Discussion

The superiority of combined cisplatin/topotecan over single-agent cisplatin in terms of response rate, PFS and OS in cervical cancer was established in the GOG179 study, but this therapeutic approach is nonetheless characterized by high levels of haematological and renal toxicity (10). In the current study with a carboplatin/topotecan regimen, myelotoxicity was also predominant, including grade 3-4 pancytopenia and febrile neutropenia, and ultimately resulted in premature closure of the study. While there were no toxic deaths, 75% of patients treated at the recommended dose experienced serious adverse events very soon after treatment initiation (mostly within the first two treatment cycles). A prior GINECO trial for advanced cervical cancer in which patients were treated with combined cisplatin, topotecan and cetuximab, was also prematurely closed in light of severe toxicity, including infection and myelotoxicity (17). Proposed reasons for this poor tolerance included a possible pharmacokinetic interaction between cisplatin and topotecan, potentially favoured by risk factors for renal failure, as well as a hypothetical interaction between topotecan and cetuximab. However, this is unlikely to be the case in the present study, as not only is carboplatin not associated with renal toxicity but in addition, patients were carefully screened prior to study enrolment, and were not included if they were presented with pre-existing renal insufficiency that might have reduced topotecan elimination through renal dysfunction or chronic infection.

Several studies following other indications have reported toxicity limitations with the carboplatin AUC5/topotecan combination. Studies of ovarian cancer patients receiving topotecan combined with carboplatin, both in front-line and salvage therapy reported limiting toxicity (18, 19). In the phase I-II trial reported by Rose *et al.*, haematological toxicity limited topotecan dose escalation with the weekly topotecan schedule of administration. The recommended combination dose was topotecan at 2 mg/m^2 days 1 and 8, every 3 weeks with carboplatin AUC5 (19). Similarly, in a recent phase II study in ovarian cancer patients combining topotecan 2.5 mg/m^2, days 1 and 8 with carboplatin AUC5 every 3 weeks, patients had significant haematological toxicity, with 40% grade 3-4 neutropenia (14). Dose reductions and delays resulted in suboptimal topotecan exposure, potentially negatively impacting efficacy. A recent report from the North Central Cancer Treatment Group (NCCTG), published during our study, evaluating combined carboplatin AUC5 with 2 mg/m^2/day oral topotecan for 5 days every 3 weeks in extensive stage small cell lung cancer was prematurely closed due to excessive toxicity (20). The authors concluded that this regimen could not be recommended in light of the excessive toxicity, with 85% grade 3-4 haematological events and four fatalities including three due to febrile neutropenia.

Whether treatment using a further reduced weekly dose of topotecan could be translated into anti-tumour activity is unknown, as the proposed lower topotecan dose (2.7 mg/m^2) was not investigated following the recommendation of the Independent Safety Data Committee to close accrual in the study. Preliminary evidence of activity of the weekly oral topotecan/carboplatin combination appears to be in line with other combinations (21). It is possible that in combination with carboplatin, the therapeutic index of oral topotecan is too low to achieve concomitant efficacy complimented with good tolerance.

Taken together, these data indicate that combination of weekly oral topotecan with carboplatin is highly toxic in women with advanced or recurrent cervical cancer. To determine whether this combination can be exploited for treatment of this disease, future trials need to focus on alternative combination schedules and alternative combinations, including more recently developed drugs.

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