Cetuximab, topotecan and cisplatin for the treatment of advanced cervical cancer: A phase II GINECO trial


Objective. Cisplatin (Cp) plus topotecan (Tc) is the first combination chemotherapy to demonstrate a survival advantage over cisplatin alone in advanced cervical cancer. Combining Cp and Tc with an epidermal growth factor receptor (EGFR) inhibitor such as cetuximab (Ce) may increase the activity of chemotherapy.

Methods. Patients with advanced cervical squamous cell cancer or adenocarcinoma and at least one measurable target received intravenous Cp 50 mg/m² on day 1 plus Tc 0.75 mg/m²/day from days 1 to 3 every 3 weeks combined with Ce (initial dose of 400 mg/m² followed by subsequent weekly dose of 250 mg/m²). Objective response rate according to RECIST criteria was the primary end point; safety, progression free survival (PFS) and overall survival (OS) were secondary end points.

Results. Between April and July 2007, 19 out of the 44 planned patients were accrued before the study was stopped early due to excessive toxicity. The most frequent adverse event was severe myelosuppression with grades 3–4 neutropenia (72%), grades 3–4 thrombocytopenia (61%), and grade 3 anemia (44.5%). The main grades 3–4 non-hematologic toxicities were infection (39%) and febrile neutropenia (28%), skin reactions (22%), renal toxicity (11%), and pulmonary embolism (11%). Five (28%) patients died during the treatment including 3 deaths related to treatment toxicity. Six (32%) evaluable patients achieved a partial response. The median times of PFS and OS were 172 and 220 days, respectively.

Conclusion. In this phase II trial, the combination Cp–Tc–Ce induced a high rate of serious adverse and/or fatal events at standard dose and schedule. Cetuximab plus platinum-based combination chemotherapy should be further explored with caution in the future in advanced cervix cancer.

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Introduction

Despite a continuously decreasing incidence in Western countries, cancer of the cervix still remains a public health concern worldwide. Systematic population screening has strongly impacted mortality, since nowadays, the majority of patients are diagnosed with early-stage cancer and are amenable to cure. However, some patients still do not participate in screening programs, and others experience a cancer relapse despite having received adequate treatment. The 5-year overall survival rate for advanced or relapsed cervical cancer is poor, ranging from 10 to 20%.

Cisplatin monotherapy had been the gold standard chemotherapy for advanced cervical carcinoma (ACC) until the combination of cisplatin and topotecan demonstrated higher efficacy in terms of response rate, disease-free survival and overall survival [1].

The epidermal growth factor receptor (EGFR) is a transmembrane receptor that binds a variety of ligands, including epidermal growth factor (EGF), transforming growth factor α (TGF-α) and others. EGFR has a tyrosine kinase activity that links the receptor to the membrane/nucleus transduction signaling cascade [2]. EGFR is expressed in cervical cancer cells, and despite some contradictory results, its expression level has been linked to prognosis and tumor aggressiveness [3–8]. EGFR is a target for several new anticancer agents,
including cetuximab, a monoclonal antibody that targets the extra-
cellular domain of EGFR. In addition to colon cancer, cetuximab
(ERBITUX™) is approved in head and neck squamous cell carcinoma,
an equally predominant histology in cervical cancer [9].

On the basis of these data, we decided to investigate the efficacy
and tolerability of a combination of cisplatin, topotecan and
cetuximab in advanced or relapsed cervical cancer.

Materials and methods

Patients

This was an open-label, uncontrolled, multicenter phase II trial,
conducted in 13 French centers. Patients were eligible for the study if
they fulfilled the following inclusion criteria: age ≥18 years, ECOG
(Eastern Cooperative Oncology Group) performance status (PS) ≤2,
histologically proven advanced cervical cancer (squamous-cell cancer
or adenocarcinoma) not amenable to curative treatment with surgery
or chemoradiotherapy, at least one measurable target lesion outside a
prior radiation field, a free interval from any prior radiation/
radiochemotherapy of more than 6 months and an absolute
neutrophil count ≥1.5×10⁹/L, platelets count ≥100×10⁹/L, total bilir-
ubin ≤1.5× upper limit of normal (ULN), ASAT, ALAT ≤3× ULN or
≤5× ULN in the setting of liver metastases and calculated creatinine
clearance (Cockroft) ≥50 mL/min. Exclusion criteria included: any
prior chemotherapy except in combination with radiotherapy, brain
metastases, any other malignancy within the past 5 years except for
adequately treated basocellular or spinocellular skin cancer, any
history of skin pathology, Crohn’s disease, ulcero-hemorrhagic colitis,
peripheral neuropathy or hearing loss ≥grade 2 according to
Common Terminology Criteria for Adverse Events version 3.0
(CTCAE V3.0), pregnancy or breast feeding or any condition that
could interfere with the study according to the investigators.

The study protocol was approved by ethics committee and was
conducted in accordance with the Declaration of Helsinki and Good
Clinical Practice guidelines. All patients provided written informed
consent before entry onto the study.

Treatment

Cetuximab was administered as an intravenous infusion before
topotecan and cisplatin, as an initial 2-hour infusion of 400 mg/m²
(day 1 of course 1), followed by weekly 1-hour infusions of
250 mg/m². Patients received pretreatment with antihistamines.
Patients remained under observation throughout the infusion and
for 1 h afterwards. Topotecan was administered as a 30 min infusion
of 0.75 mg/m²/day on days 1, 2 and 3, followed by cisplatin as a 1-
hour infusion of 50 mg/m² on day 1, repeated every 21 days.
Concomitant medications included antiemetic drugs (anti-5HT3 and
steroids). Saline hyperhydration starting 12 h before cisplatin
infusion, and continuing for 12 h after was recommended.
Cetuximab was administered until disease progression or unaccep-
table toxicity. Six cycles of topotecan plus cisplatin was adminis-
tered but treatment could be continued for responder or stabilized
patients.

The use of hematopoietic growth factors (lenograstim 150 µg/day)
was considered in case of grades 3–4 or febrile neutropenia at the
previous chemotherapy cycle, or in the curative setting in case of
grades 3–4 febrile neutropenia. Erythropoietin support (Epoietin Bêta
™) is approved in head and neck squamous cell carcinoma,
requiring platelet transfusion. A further dose level reduction
of inadequate blood cell count at day 29, the next cycle had to be
delayed until blood count recovery, and the topotecan dose had to be
decreased by one level.

Cetuximab had to be interrupted for up to 2 weeks in the case of
grade ≥3 skin reactions. Patients were to be rechallenged with
the same dose if toxicity resolved to grade 2. In case of subsequent grade
≥3 toxicity, cetuximab administration was delayed and dose reduc-
tion to 200 mg/m², and ultimately 150 mg/m² had to be considered.
Recurrence of a grade ≥3 skin reaction despite two dose reductions
warranted discontinuation of cetuximab. Grades 1–2 reactions only
required topical or systemic tetracyclines, that were also recom-
mended in case of higher grade toxicity. In case of unacceptable
chemotherapy-associated toxicity, patients benefiting from therapy
could continue to receive cetuximab as a single-agent.

Pretreatment assessments, response and toxicity evaluations

All patients underwent pretreatment screening 2 weeks before the
start of the study, including full medical history, physical examination,
determination of PS, laboratory values, disease staging history,
computed tomography (CT) or magnetic resonance imaging (MRI)
scans of target lesions (≤4 weeks before the start of the study). Tumor
response was assessed every 2 cycles according to Response
Evaluation Criteria in Solid Tumors (RECIST) criteria [10] by the
same modality (CT or MRI) used for baseline evaluation. Adverse
events were recorded according to CTCAE v3.0 at each weekly visit
before treatment administration. Follow-up assessments were made
4 weeks after the last dose of study medication and every 3 months
thereafter.

Statistical analyses

The study was planned to test an estimated rate of objective
response of 35% with a type I error (α) of 0.05 and a power of 85%
(1−β). This hypothesis required a sample size of 44 patients,
assuming that 10% of patients would not be assessable.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median/N</th>
<th>Percent or (range)</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
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<td>(37–71)</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td>(31%)</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>(53%)</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>(16%)</td>
</tr>
<tr>
<td>Cell type</td>
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<td></td>
</tr>
<tr>
<td>Squamous-cell</td>
<td>14</td>
<td>(74%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>5</td>
<td>(26%)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>(26%)</td>
</tr>
<tr>
<td>2</td>
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<td>(37%)</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>(37%)</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>4</td>
<td>(21%)</td>
</tr>
<tr>
<td>IIIB</td>
<td>6</td>
<td>(32%)</td>
</tr>
<tr>
<td>IV</td>
<td>8</td>
<td>(42%)</td>
</tr>
<tr>
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<td>1</td>
<td>(5%)</td>
</tr>
<tr>
<td>Prior cisplatin (radiosensitizing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>(58%)</td>
</tr>
<tr>
<td>No</td>
<td>8</td>
<td>(42%)</td>
</tr>
<tr>
<td>Site of diseasea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvis</td>
<td>2</td>
<td>(11%)</td>
</tr>
<tr>
<td>Distant</td>
<td>9</td>
<td>(50%)</td>
</tr>
<tr>
<td>Both</td>
<td>7</td>
<td>(35%)</td>
</tr>
</tbody>
</table>

* 1 patient had no target lesion.
Progression-free survival was calculated from the first day of treatment to the date of progression or death or any cause. The overall survival was defined as the time from the onset of treatment until death from any cause, or loss to follow-up. Progression-free and overall survival were described using the Kaplan–Meier estimates method.

Efficacy analyses were conducted on the intent-to-treat (ITT) population. Statistical analyses were carried out using SPSS, version 15.0.

Results

Between April and July 2007, 19 out of the planned 44 patients were enrolled in the study from 13 centers before the study was closed due to excessive toxicity.

The patients’ characteristics are described in Table 1. One patient never started therapy leading to an ITT population of 18 patients. A total of 54 chemotherapy cycles were administered. Two (11%) patients completed the planned 6 cycles of chemotherapy and treatment was stopped for three (17%) patients due to disease progression, one (5%) patient for an intercurrent disease, six (33%) for toxicity, and for the remaining 6 patients after the recommendation by the independent safety data committee (ISDC) to stop the study.

Toxicity

As the study was ongoing, an unexpected excess of mortality was reported to the study sponsor and the study coordinator who immediately decided to suspend any further patient accrual while waiting for a statement from the ISDC. Comprehensive data monitoring on the 19 accrued patients was undertaken. From these data, the ISDC concluded that the study should be stopped due to an excess of mortality. Myelosuppression was the most frequent severe toxicity observed with grades 3 and 4 neutropenia and thrombocytopenia occurring in more than half of the patients. The most frequent severe toxicity observed with grades 3 and 4 thrombocytopenia occurred in 61% of patients. Two (11%) patients had grades 3 or 4 renal toxicity and 2 (11%) patients experienced pulmonary embolism. Grade 3 skin reactions were observed in 4 (22%) patients.

Among the 54 chemotherapy cycles, treatment delay occurred in 8 (15%), mostly because of neutropenia (6 cycles). Out of the 18 patients who received study treatment, 13 had to be hospitalized for toxicity events, accounting for a total of 20 hospitalizations of a median duration of 7.8 days. Supportive therapies were intensively administered, including hematopoietic growth factors, antibioticotherapy, blood and platelets transfusions or erythropoietin. Five (28%) patients died during treatment: two patients died from sepsis in the setting of grade 4 neutropenia and thrombocytopenia, clearly attributable to the treatment, one patient died from pulmonary embolism with relationship to treatment considered as “possible”, another patient died from acute respiratory distress syndrome related to an inhalation pneumopathy that was considered as an intercurrent disease and not study-related according to the investigator. The remaining patient died from disease progression.

Efficacy

The primary end point of this study was response rate, which was assessed in an ITT analysis. A partial response was achieved in 6 (32%) patients and stable disease in 6 (32%). Two (10%) patients were not evaluable for efficacy, but were included in the ITT analysis: one patient withdrew her consent before receiving any treatment and another patient had no measurable lesion at baseline. Three (16%) patients had progressive disease and two patients died from toxicity during the first cycle.

The median PFS and OS were 172 and 220 days, respectively (Fig. 1).

Discussion

Objective response rate was the primary end point of our trial, in an attempt to evaluate a potential benefit from the combination of cetuximab with the chemotherapy regimen combining cisplatin plus topotecan in patients with advanced cervical cancer. The study was however premature closed as a result of an unexpectedly high incidence of severe toxicity and patient death.

Hematologic toxicity profile by patient (%)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>CTCAE grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (28%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>1 (5.5%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>–</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>–</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>–</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Renal</td>
<td>1 (5.5%)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>6 (33.5%)</td>
</tr>
<tr>
<td>Other gastro-intestinal</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Pain</td>
<td>8 (44.5%)</td>
</tr>
<tr>
<td>Neupathy</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Skin reactions</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5 (28%)</td>
</tr>
</tbody>
</table>

Table 3

Non-hematologic toxicity profile by patient (%)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>CTCAE grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>1 (5.5%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>–</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>–</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>–</td>
</tr>
<tr>
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<td>3 (17%)</td>
</tr>
<tr>
<td>Renal</td>
<td>1 (5.5%)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
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<tr>
<td>Other gastro-intestinal</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Pain</td>
<td>8 (44.5%)</td>
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<tr>
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<tr>
<td>Skin reactions</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5 (28%)</td>
</tr>
</tbody>
</table>

Fig. 1. Progression free and overall survivals.
Long et al. comparing cisplatin–topotecan to cisplatin alone in 294 ACC patients, the cisplatin–topotecan regimen presented definite hematologic toxicity with grades 3–4 neutropenia and thrombocytopenia observed in 70% and 31% of patients, respectively [1]. Though the restricted number of patients accrued in our study limits comparison, there is a slight trend for higher rates of grade 4 neutropenia (61% versus 46%) and grades 3–4 thrombocytopenia (61% versus 31%) in our study. However the main differences between the two studies are the consequences of the severe hematotoxicity observed. In our study with cisplatin–topotecan–cetuximab, 56% of patients experienced severe infection or febrile neutropenia, whereas it was the case in only 18% of patients with the cisplatin–topotecan combination in Long et al. study. Five out of 18 (28%) patients died during treatment in our study including three treatment-related deaths.

These data raise the question of a potential role of cetuximab in increasing the myelosuppression and its adverse consequences induced by the cisplatin–topotecan regimen. However, there is no evidence that cetuximab as a single agent is myelotoxic per se [11]. When combined with cisplatin, cetuximab has not been shown to enhance cisplatin induced myelosuppression [12]. The sequential combination of cetuximab and topotecan was explored in vitro and in vivo on mice models bearing xenografts from ovarian, breast and colon cancer cell lines. In these experiments, the combination resulted in prolonged survival as compared to each drug alone without additional signs of acute or delayed toxicity [13]. In patients with metastatic colorectal cancer the doublet of cetuximab with irinotecan, another topoisomerase I inhibitor, yielded rates of 9.4% and 0.5% of grades 3–4 neutropenia and thrombocytopenia, respectively, that is consistent with single-agent irinotecan toxicity [14]. In contrast, an increased incidence in grade 4 neutropenia (50% versus 37% of patients) was observed when cetuximab was added to the cisplatin–vinorelbine regimen in a randomized phase II study of 86 stage IIIb/IV non-small cell lung cancer patients, but the occurrence of severe infection was low in both regimens [15]. In addition, an increased number of sepsis cases but without myelosuppression enhancement was observed when cetuximab was added to another cisplatin doublet (cisplatin plus fluorouracil) in a randomized study of 442 patients with advanced squamous-cell carcinoma of the head and neck [16].

One alternative hypothesis for the increased toxicity with the cetuximab–cisplatin–topotecan combination might be that the patients accrued in our study had a worse condition than in previously reported studies. Most of the patients included in our study, similarly to the GOG-179 trial, had good ECOG performance status of 0 and 1, and 58% had prior cisplatin administration (as a radiosensitizer) [11]. However, our patients had more extensive disease both initially (stage IV: 42% of patients in present study versus 12% in GOG-179) and at time of randomization (distant metastases: 89% versus 56%), reflecting their poorer prognostic and perhaps enhanced fragility. We also had hypothesized that an initial decrease in renal function, possibly worsened by cisplatin administration immediately prior to that of topotecan, might have increased the area under the curve of this latter drug, thus increasing myelosuppression. Initial renal function evaluation shows that 74% of our patients had a pre-treatment creatinine clearance equal or over 60 mL/min, whereas 5 patients had a moderate renal function alteration with creatinine clearance value ranging from 45 to 59 mL/min.

Out of the 6 patients who stopped therapy for toxicity reasons, 3 had initial creatinine clearance below 60 mL/min (59.5, 56 and 48.5 mL/min, respectively). In addition, pre-existing hydroponephrosis, pre-existing nephropathy, or the presence of J-J probes favoring urine reflux were found in 4 of these patients, among whom two developed renal failure in the setting of septic shock.

Whatever the reason for the excessive toxicity observed in this study, this trial stresses the importance of performing adequate phase I study before embarking into phase II trial. In the light of the absence of overlapping toxicity between cetuximab and chemotherapy, and the safety of cisplatin–cetuximab or irinotecan–cetuximab regimens, we did not feel mandatory a cetuximab–cisplatin–topotecan combination phase I study before launching the phase II. This trial shows that unexpected toxicity might occur as soon as targeted agent is added to chemotherapy agents. This observation will be taken into account for future GINECO studies in collaboration with ethics committees.

In spite of the considerable toxicity observed in this phase II trial that obviously impacted treatment duration, 6 partial responses (32% overall response rate) were observed, suggesting the potentially high efficacy of combining cetuximab with chemotherapy in ACC.

The incorporation of targeted therapies is certainly a promising axis of clinical investigation in advanced cervical cancer, and cetuximab should be further investigated. The high rate of severe hematotoxicity with an excess of mortality during the trial resulting in premature termination of this phase II trial suggests that cetuximab-chemotherapy combinations in cervical cancer should be explored in a selected population of patients with better condition and/or with chemotherapy different from the cisplatin–topotecan regimen at standard dose and schedule. Topotecan dose could be reduced or another active regimen could be combined with cetuximab to further explore this concept.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

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References


