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A prospective phase II study of topotecan (Hycamtin®) and cisplatin as neoadjuvant chemotherapy in locally advanced cervical cancer

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ABSTRACT

Objectives. To evaluate the feasibility, toxicity and activity of neoadjuvant chemotherapy (NACT) using cisplatin and topotecan in patients affected by locally advanced cervical cancer (IB2–IIIB).

Methods. Patients with histologically confirmed FIGO stage IB2–IIIB uterine cervical cancer were treated with topotecan 0.75 mg/m^2/day (days 1–3) followed by cisplatin 75 mg/m^2 (day 1), every 21 days for three consecutive cycles. After the last cycle of chemotherapy, within 3 or 4 weeks, patients underwent radical surgery with lymph node dissection.

Results. In the years 2007–2010, 46 women were enrolled into the study. Hematologic toxicity was the most relevant side effect. Thirty-eight patients (82.6%) underwent radical surgery after neoadjuvant chemotherapy (NACT) and were assessable for pathologic responses; surgery was not performed in 8 (17.4%) non-responder patients or with progression disease. Objective pathological response was recorded in 34 patients (89.5%); 6 patients (15.8%) achieved a complete response (CR), 28 (73.7%) patients achieved a partial response (PR); stable disease (SD) occurred in 2 patients (5.3%) with IIA initial disease and progression disease (PD) was registered in 2 patients (5.3%) with IIIB initial disease. The cumulative 2-year progression free survival (PFS) and overall survival (OS) of the 46 enrolled patients in the study were 70% and 81%, respectively; the 2-year PFS and OS of the 38 operated patients were respectively 79% and 95%.

Conclusions. The cisplatin–topotecan combination seems to be feasible and with an acceptable toxicity profile and a promising response rate for the treatment of locally advanced cervical cancer (LACC). Phase II and III studies are needed to compare this combination with other platinum-based chemotherapeutic associations.

1. Introduction

Cervical cancer is still one the most widespread gynecological malignancy in women worldwide [1]. The crude incidence of cervical cancer in the European Union is 13.2/100,000 with a crude mortality rate of 5.9/100,000 [2]. Remarkably, the incidence and mortality rates associated with cervical cancer are higher among minorities, reaching 3% and 2% of cancer deaths in Hispanics and African American women, respectively [3].

The treatment for uterine cervix cancer is strictly related to the stage of disease. Since the early 1980s the high chemo-sensitivity of this cancer was definitively clear and chemotherapy started to be strongly recommended. Chemotherapy was suggested for the control of systemic disease before surgery (neoadjuvant chemotherapy–NACT) or in combination with radiotherapy, as adjuvant treatment after surgery or for palliative care.

Actually, several controversies still exist for the management of locally advanced cervical cancer, which represents almost 60% of all diagnosed cervical cancers tumors, with a 2- and 5-year overall survival ranging from 88% to 75% for stage IB2 and from 59% to 41% for stage IIIB [4]. In 1999, a National Cancer Institute Alert [5] recommended that concurrent chemo-radiation should be considered instead of radiotherapy alone in women with cervical cancer. On the other hand, in a subsequent meta-analysis was found that NACT followed by surgery is superior to radiotherapy alone in terms of overall survival [6].

The rationales for the use of NACT are several. Tumor-size reduction may facilitate subsequent local therapy, both for radiotherapy or surgery, transforming inoperable tumors into radically resectable ones. Furthermore, it treats also the micrometastatic dissemination of disease, preventing a significant proportion of relapses [7].

Cisplatin has been established to be the most effective cytotoxic drug against cervical carcinoma [8]; recently many cisplatinum-based combinations have also been investigated [9,10].

It has been found that even in absence of survival improvement, several cisplatinum-based combinations achieve higher overall

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clinical response rate [11,12], reaching up to 73–95% [13] but with the inconvenience of higher haematologic and nonhaematologic toxicity rates [10,11].

One of the most investigated and encouraging combinations is the association of cisplatinum and topotecan, a topoisomerase I inhibitor, which has shown a significant benefit for survival, with acceptable toxicity profile, in the setting of recurrent and advanced cervical cancer [14].

In the present pilot phase II trial we want to investigate if the combination of cisplatin and topotecan may improve the operability and pathological response rates in chemotherapy-naïve patients affected by locally advanced cervical cancer (stage IB2–IIIB), also acquiring the adverse effect profile of this new schedule. We include patients with IB2 and IIA bulky disease considering the high potential for receiving adjuvant radiotherapy/chemoradiotherapy to which these patients are subjected after receiving primary definitive surgical approach [15]. Up to now, no previous experiences with this association in the neoadjuvant chemotherapy setting for LACC have been reported in English literature.

2. Materials and methods

Between April 2007 and August 2010, patients with a histologically proven diagnosis of invasive carcinoma of the uterine cervix were enrolled into the study.

Institutional review board approval (N°317/07, 20th April 2007) was obtained at the Policlinico Umberto I "Sapienza" University of Rome.

Eligibility was restricted to patients with squamous, adenosquamous and adenocarcinoma of uterine cervix diagnosed at FIGO stage IB2–IIIB. Additional inclusion criteria were as follows: (1) lesion recognized and staged through physical and gynaecologic examination under anesthesia, pelvic examination and/or abdomino-pelvic CT scan and/or diagnostic laparoscopy, and/or cystoproctoscopy, and/or pelvic MRI; (2) normal haematologic, renal, hepatic function as determined by hemoglobin >9 g/dl; neutrophil >1500/μl; platelet count more than 100,000/μl; creatinine <1.5 mg/dl and/or creatinine clearance >60 ml/min, AST (aspartate transaminase) and ALT (alanine/transaminase) less than 1.5× normal upper limit; (3) no heart or lung disease by clinical examination; (4) no active infection; (5) Easter Cooperative Oncology Group (ECOG) Performance Status <2 [16]. The patients were also required to sign an informed consent before entering into this study.

Reasons for ineligibility included (1) concomitant malignancies, except basocellular or spinocellular skin carcinoma during last 5 years; (2) bilateral hydroureteronephrosis not solving by ureteral stent or percutaneous nephrostomy and with abnormal creatinine level; (3) allergy to analogues of camptothecin; (4) and infection, severe systemic disease limiting treatment feasibility; SNC disease; pregnancy or lactation.

Staging was defined according to the International Federation of Gynaecology and Obstetrics (FIGO). Before starting administration, all patients were evaluated with clinical examination plus radiologic, haematologic and biochemical assessments. All patients were submitted to a gynaecologic examination under general anesthesia. Abdomino-pelvic CT scan was performed in all patients as it provides useful informations for parametrial, lymphatic, and visceral extent. Use of cystoscopy was limited to patients with suspected advanced disease at gynaecological examination or having suspicious invasion on CT scan. Magnetic resonance was indicated in adjunction to CT scan when entophytic lesions difficult to measure were detected with gynaecological examination because of its major role in determining whether a patient surgical candidate by excluding parametrial involvement [17]. If peritoneal washing or peritoneal biopsies performed through laparoscopy resulted positive for neoplasia, the stage of disease was altered. Para-aortic nodes were considered second station of drainage of cervix uteri and were considered distant metastasis. After clinical staging, neoadjuvant chemotherapy was administered according to the following schedule:

Topotecan (Hycamtin®; GlaxoSmithKline, Philadelphia, PA) 0.75 mg/m^2/day intravenously (IV) during 30 min days 1, 2 and 3, followed by cisplatin 75 mg/m^2/day 1 repeated every 21 days. Three consecutive cycles were planned. Before cisplatin was administered, patients received IV hydration with 1 l of fluids (NaCl solution 500 ml and 5% glucose solution 500 ml) plus KCl 20 mEq plus MgSO4 8 mEq over a 90-min period. After cisplatin was administered, patients received 1 l of fluid plus furosemide 10 mg over a 2-h period.

All patients received antiemetic prophylaxis (granisetron 1 mg and dexamethasone 20 mg) both given intravenously 30 min before treatment delivery and 3 days after per os. Prior to each cycle, patients had an interval history and physical examination, transvaginal ultrasound complete blood counts, renal and liver profiles and documentation of the largest diameter by perpendicular dimensions of measurable disease by physical examination. Toxicity was evaluated according to the World Health Organization (WHO) criteria [18]. Hematologic toxicity was evaluated by a complete hemogram on days 7–14 and 21. In case of WBC less than 3000/μl, neutrophil count less than 1000/dl and/or platelet less than 100,000/μl treatment was postponed by 1 week. If WBC less than 1000/μl, neutrophil count less than 500/dl and/or platelet less than 50,000/μl for a period longer than 5 days, or in case of any severe mucositis, the drug doses were reduced by 20% in the next cycle. Granulocyte colony-stimulating factors (G-CSF) was administered at a dose of 5 μg/kg subcutaneously daily in cases of grade 4 neutropenia up to leukocytes superior to normal. Patients with an acceptable level of toxicity were permitted to continue treatment for a maximum of five cycles after discussion with the study chair.

Preoperative pre-assessment after NACT was done by performing both a gynaecological examination and a total body CT scan; clinical response was defined according to WHO criteria [18]: complete response (CR) was defined as the complete disappearance of all macroscopic disease, whereas partial response (PR) was defined as a reduction of at least 50% in the sum of the products of largest diameters of all measurable lesions with no appearance of new lesions. Stable disease (SD) was defined as a reduction less than 50% or an increase not greater than 25% in the sum of the products of the largest two diameters of all measurable lesions with no appearance of new lesions, and progressive disease (PD) was defined as an increase greater than 25% in the sum of the products of the largest two diameters of all measurable lesions or the appearance of new lesions. Objective response rate was defined as the proportion of CR plus PR in all patients. After a median of three courses all patients deemed operable underwent radical hysterectomy and systematic pelvic lymphadenectomy within 3 or 4 weeks after the administration last cycles. Aortic node dissection was performed in the case of positive iliac nodes on frozen section or aortic metastases detected at the staging workup. Histological analysis of surgical specimens was planned to separately assess the extent of cervical vaginal and parametrial disease as well as the lymph nodal status, the involvement of surgical resection margins and the vascular space involvement.

Pathologic response was defined according to the TNM classification [19].

2.1. Statistical analysis

The study was a nonrandomized phase II study in which the sample size would provide a statistical power of 80% to detect a 25% increase in response rate. The probability of type I error was fixed at 0.05. All analyses were done on an intention to treat basis. Analyses were carried out using Sigma Plot version 10.0 Software.

3. Results

Between April 2007 and August 2010, 47 women were evaluated and 46 women were enrolled into the study; the baseline characteristics of enrolled patients are summarized in Table 1. Forty cases were