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ORIGINAL ARTICLE

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Neoadjuvant treatment of locally advanced carcinoma of the uterine cervix with epirubicin, paclitaxel and cisplatin

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Abstract *Purpose:* The present study was conducted to explore whether neoadjuvant chemotherapy with a combination of epirubicin, paclitaxel and cisplatin could improve the operability and pathological response rate in locally advanced cervical cancer patients. *Methods:* Between April 1996 and July 2000, 42 patients with carcinoma of the uterine cervix, FIGO stage Ib_2-IVa, were treated with two or three 21-day cycles of an epirubicin 100 mg/m^2, paclitaxel 175 mg/m^2, cisplatin 100 mg/m^2 regimen. *Results:* All patients were eligible for evaluation of toxicity and response. A total of 92 courses of therapy were administered. Three patients had a 20% reduction from the starting dose due to haematological toxicity. Grade 3–4 leukopenia was observed in 15% of cycles, requiring G-CSF support in half of them. Major non-haematological toxicity consisted of grade 3 alopecia (100%), and grade 3 nausea and vomiting (40%). A total of 33 clinical responses (78.5%, 95% CI 63.8–93.2) were recorded, 8 complete responses (CR) and 25 partial responses (PR). Of the 42 patients, 32 (76.2%) underwent radical surgery. At pathological examination 8 complete or microscopic pathological responses, 17 PRs, and 9 patients with stable disease were observed. The median follow-up time was 17 months for the 42 patients enrolled (range 3–62 months). Among the patients submitted to radical surgery, five recurrences were observed, with a median disease-free survival of 47 months. Median overall survival had not been reached at the time of this report. These results appear to be in the range reported for other neoadjuvant cisplatin-based regimens not including paclitaxel. *Conclusions:* Neoadjuvant chemotherapy with the epirubicin, paclitaxel and cisplatin combination followed by radical surgery proved to be a safe and effective approach to advanced cervical cancer.

Keywords Neoadjuvant chemotherapy · Cervical cancer · Cisplatin · Epirubicin · Paclitaxel

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Introduction

Whereas it is generally accepted that radical surgery or radiotherapy can be curative for the majority of patients with early-stage cervical cancer [13], there is no agreement on the best approach to locally advanced disease, whose prognosis remains very poor, in spite of the therapeutic advances achieved in recent years [32].

In the last two decades, several studies have demonstrated that up-front chemotherapy can reduce tumour bulk, making radical surgery feasible, sterilize distant foci of disease, and decrease the incidence of lymph node metastases [1, 2, 3, 12, 34]. Thus neoadjuvant chemotherapy followed by radical surgery has become one of the novel approaches to the cure of locally advanced disease, although its precise role needs to be further defined. Historically, cisplatin has been considered the most effective drug in the treatment of cervical cancer, achieving objective responses in 20–85% of patients [7, 30]. In order to improve the response rate obtained by this compound, when used as a single agent, several drug combinations have been tested, but have shown considerable toxic effects and have failed to demonstrate significant improvements in clinical response, with the exception of early-stage and/or small-volume cervical cancer.

More recently, the significant activity shown in other gynaecological malignancies, such as ovarian, breast and endometrial cancer, and in several squamous cell carcinomas, such as head and neck and lung cancers [29], has focused interest on paclitaxel. The clinical trials performed on squamous cell cervical cancer patients with paclitaxel, either as a single agent [15, 31] or in

combination with cisplatin [20, 25, 26], have placed this compound among the most active drugs in this disease, and studies on the possible synergistic interactions between cisplatin and paclitaxel have suggested a sequence dependency of these two drugs [28].

Among the other agents tested, anthracyclines have demonstrated activity in up to 20% of treated patients [8, 24, 35]. Paclitaxel and epirubicin have different mechanisms of action, and there is no evidence of clinical cross-resistance between these two compounds. For these reasons, the present study was conducted to explore whether the combination of epirubicin, paclitaxel and cisplatin, in a dose regimen which had already proved to be safe and effective in ovarian cancer patients [9], may improve the operability and pathological response rate in chemotherapy-naive patients affected by locally advanced cervical cancer.

Patients and methods

Eligibility

Patients with histologically confirmed, locally advanced (FIGO stages Ib_2-IVa, >4 cm) cervical cancer were eligible for the study. Further entry criteria were: age >18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, life expectancy >12 weeks, patient informed consent, white blood cell (WBC) count $\geq 3{,}5\times10^9$/l, platelet (PLT) count $\geq 150\times10^9$/l, and bilirubin and creatinine levels less than 1.5 times the upper limit of normal. Patients were ineligible with: prior malignancy (except for adequately treated non-melanoma skin cancer or ovarian borderline tumour), previous radiotherapy or chemotherapy, resting left ventricular ejection fraction (LVEF) <60% and/or cardiological contraindications to the use of paclitaxel and/or epirubicin, and active infection or major medical illness. Staging was done according to the International Federation of Gynaecology and Obstetrics (FIGO). Pretreatment evaluation consisted of general and gynaecological examination under general anaesthesia, colposcopy, abdominal-pelvic magnetic resonance imaging (MRI) and chest radiography. Cystoscopy and sigmoidoscopy were performed when indicated.

Study design

After clinical staging, neoadjuvant chemotherapy was administered on day 1 of 3-weekly cycles according to the following schedule: epirubicin 100 mg/m^2 intravenously (i.v.), paclitaxel 175 mg/m^2 i.v., cisplatin 100 mg/m^2 i.v. Two consecutive cycles were planned. After the completion of chemotherapy, patients were reassessed according to the above criteria. WHO response evaluation criteria were adopted. A third cycle was given to stage III-IVa patients showing at least a minimal response after the first two cycles. In the case of no change or progression of disease, inoperable patients were considered for exclusive radiotherapy. In operable patients, type III-V [23] radical hysterectomy with systematic pelvic lymphadenectomy was performed within 30 days of the completion of chemotherapy. Aortic node dissection was performed in the case of positive common 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 node status and the involvement of surgical resection margins.

Treatment

Epirubicin was administered first by rapid freely running i.v. infusion. Paclitaxel was then administered as a 3-h i.v. infusion followed by cisplatin as a 2-h i.v. infusion with adequate pre- and posthydration. All patients received standard premedication with 20 mg dexamethasone given orally 12 and 6 h before paclitaxel, and 300 mg cimetidine plus 50 mg diphenhydramine given i.v. 30 min prior to paclitaxel. All treatments were repeated every 3 weeks. Granulocyte colony-stimulating factor (G-CSF) was administered at a dose of 5 μg/kg subcutaneously daily in cases of WBC less than 1500/μl and continuing until the reversal of neutropenia. All patients received antiemetic prophylaxis (granisetron) prior the administration of, and 3 days after, chemotherapy. Complete blood count and PLT count plus a routine 12-channel biochemistry were performed twice weekly. Chemotherapy-induced toxicity was graded according to the National Cancer Institute common toxicity criteria [17]. In the case of WBC less than 3000/μl and/or PLT less than 100,000/μl, treatment was postponed for 1 week. In the patients in whom treatment was delayed for more than 2 weeks, neoadjuvant treatment was discontinued. If WBC was less than 1000/μl or PLT less than 50,000/μl for a period longer than 5 days, or in cases of any severe (grade 3-4) mucositis, the drug doses were reduced by 20% in the next cycle.

Statistical analysis

Disease-free survival (DFS) was defined as the period from radical surgery until the date of the first documented evidence of local or distant recurrence or the date last seen, while overall survival (OS) was calculated from diagnosis until death or date last seen. Medians and life tables were analysed with the product-limit estimate of Kaplan and Meier [10]. DFS analysis was performed using SOLO statistical software (BMDP Statistic Software, Los Angeles, Calif.).

Results

Between April 1996 and July 2000, 42 patients were entered into this study. All patients were evaluable for toxicity and response. Patient characteristics are listed in Table 1. A total of 92 courses of therapy were administered, with only eight patients receiving three cycles according to the study protocol.

Table 1 Patient characteristics

		%
Patients	42	100
Age (years)		
Median	53	
Range	30–75	
FIGO stage		
Ib_2	7	18
IIa >4 cm	3	7
IIb	21	50
IIIa	1	2
IIIb	7	18
IVa	3	5
Lymph node status[a]		
Negative	22	52
Positive	20	48
Histology		
Squamous	31	74
Adenocarcinoma	11	26
Grade of differentiation		
1	2	5
2	17	40
3	23	55

[a]Assessed by MRI

Severe haematological toxicity consisted of neutropenia in 24% of patients (grade 3 12%, grade 4 3% of cycles, requiring G-CSF support in half of them). Due to grade 4 haematological toxicity in the first cycle, three patients (7%) had a 20% dose reduction in the following courses. Major non-haematological toxicity consisted of grade 3 alopecia (100%) and nausea/vomiting (40%).

Following completion of chemotherapy, 33 clinical responses (78.5%, 95% CI 63.8–93.2) were recorded. In particular, there were 8 (19%) complete responses (CR) and 25 (59.5%) partial responses (PR). In Table 2 the clinical responses are detailed according to stage. Four patients (9.5%) progressed and five (12%) showed stable disease. Of these, one 30-year-old patient with stage Ib_2 cancer, and clinical/radiological stable disease but showing subjective improvement, underwent radical surgery. The remaining eight patients were submitted to radiation therapy, all further progressing during salvage treatment. As expected, the CR rate was higher in the less-advanced stage subset (Ib_2-IIb, 25.8%), compared with stage III-IVa patients (0%).

A total of 34 patients underwent laparotomy, radical surgery being performed in 32 (76.2%; stages Ib-IIb 97%, stages IIIa-IVa 36%). In two patients (both stage IIIb, one endometrioid adenocarcinoma) radical surgery was abandoned due to the presence of intraperitoneal spread of disease. A type III radical hysterectomy was performed in 22 patients (68.8%), a type IV in 7 (21.9%), and type V in 2 (6.2%), while an anterior pelvic exenteration was required in one stage IVa patient (3.1%). The average numbers of pelvic and aortic nodes resected per patient were 51 (range 29–94) and 13 (range 2–25), respectively. There was no excess perioperative morbidity compared with that observed in our previous institutional series [4]. Surgical resection margins were tumour-free in all cases. At pathological examination, response was confirmed in 25 of the 32 patients undergoing radical surgery (78.1%), while stable disease was observed in 9 (Table 3). Of the pathological responses, only one (squamous cell carcinoma, stage IIb) was complete, while a further seven patients showed microscopic residual tumour in the cervix. Of these patients, one also showed microscopic metastasis in one internal iliac lymph node. Therefore, histological analysis revealed an ''optimal'' response in 25% of patients undergoing radical surgery. Overall, seven pathological responses were recorded among the adenocarcinomas (63.6%).

Of the 20 patients with positive lymph nodes at staging evaluation, 11 (55%) responded clinically and underwent radical surgery, but in 7 of them (63%) node metastases were pathologically confirmed.

The median follow-up was 17 months for the 42 patients enrolled (range 3–62 months). Among the patients submitted to radical surgery, five recurrences (four local, one distant) were observed, only one of them in a patient with a pathological ''optimal'' response, after a 48-month disease-free interval. Median DFS was 48 months. Two patients died of disease. Median OS had not been reached at the time of this report.

Discussion

The treatment of advanced carcinoma of the uterine cervix is still a clinical challenge. In the present study, the efficacy of an epirubicin, paclitaxel and cisplatin combination in a subset of patients with advanced cervical cancer was tested for the first time. This regimen was found to be feasible but with substantial toxicity. Nevertheless, chemotherapy-induced side effects were easily manageable with, as expected, no impact on

Table 2 Clinical response according to stage

FIGO stage	No. of patients	Complete response	Partial response	Stable disease	Progression
Ib_2-IIa	10	2	7	1	–
IIb	21	6	12	1	2
IIIa	1	–	1	–	–
IIIb	7	–	4	2	1
IVa	3	–	1	1	1
Total (%)	42 (100)	8 (19.0)	25 (59.5)	5 (12.0)	4 (9.5)

Table 3 Pathological responses according to stage

FIGO stage	No. of patients	Complete plus microscopic pathological responses	Partial response	Stable disease
Ib_2-IIa	10	4	2	4
IIb	18	2	14	2
IIIa	1	–	1	–
IIIb	4	2	–	2
IVa	1	–	–	1
Total (%[a])	34 (100)	8 (23.5)	17 (50.0)	9 (26.5)

[a]Calculated on the patients who underwent laparotomy

perioperative morbidity. Clinical responses were seen in 78.5% of treated patients, resulting in a radical operability rate of 76.2%. These findings appear to be in the range reported for other neoadjuvant cisplatin-based regimens not including paclitaxel [5]. In particular, the percentage of "optimal" pathological response (19%) is comparable to that observed in our previous experience with a cisplatin, bleomycin, plus/minus methotrexate combination [1], and to that observed using cisplatin alone [7].

However, there are some considerations that are relevant in this respect. The characteristics of the patients in the present study seem to be markedly different from those reported in our previous studies [1, 2], and indicate a particularly poor prognosis subset. In the present series, 25% of patients were affected by stage III-IV disease, 26% by tumours with an adenomatous component, and almost half (45%) showed pelvic and/or aortic node metastases at the staging workup. The majority of patients were given two cycles of therapy, thus allowing radical surgery in responders within 2 months of diagnosis, while other studies have reached similar responses with three cycles of chemotherapy [1, 4, 6, 22, 37]. The only other study using three cycles of a paclitaxel-based neoadjuvant treatment showed higher pathological response rates, with a 16% incidence of CR and 18% of patients with only microscopic residual tumour in the cervical specimen [37]. However, that study was performed only in patients affected by squamous cell carcinoma, and with less-advanced disease (71% stage Ib-IIa >4 cm), thus with a far better prognosis than our study population.

Moreover, it remains to be established whether the encouraging results reported by Zanetta et al. [37] should be attributed exclusively to paclitaxel, since ifosfamide has also been proved to be highly effective in the treatment of cervical carcinoma, even as a single agent [29] or in combination with cisplatin [19]. In this respect, a multicentre randomized study has demonstrated that the addition of paclitaxel to the cisplatin-ifosfamide combination results in a higher "optimal" response rate in advanced cervical cancer patients [38], and another ongoing study is seeking to verify whether the paclitaxel-cisplatin combination yields similar results in the absence of ifosfamide.

In 1999, reports of five randomized studies describing the significant benefit of concurrent chemoradiotherapy in locally advanced cervical cancer [11, 16, 21, 27, 36] prompted the National Cancer Institute to affirm the clinical relevance of administering concurrent chemotherapy to patients with advanced cervical cancer requiring radiotherapeutic treatment [18]. Despite this recommendation, chemoradiotherapy is still far from being universally accepted as the gold-standard primary treatment of advanced cervical cancer, especially given the important toxic effects caused by the addition of a cytotoxic drug to the irradiation. In this respect, we have recently reported a phase I-II trial of preoperative chemoradiation followed by radical surgery [14] which showed a particularly high rate of pathological response and local control of disease, but was associated with a certain grade of acute toxicity, and intra- and postoperative complications. It should also be taken into account that the myelotoxic effects of chemotherapy may delay radiation therapy, and that tissue hypoxia consequent upon drug-related anaemia may adversely affect the efficacy of radiation therapy. In such a context, neoadjuvant chemotherapy followed by radical surgery remains a valid approach to advanced cervical cancer. Its real impact on prognosis and survival can only be clarified by large randomized trials comparing it with chemoradiation [33].

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