Concurrent radiotherapy and weekly paclitaxel for locally advanced or recurrent squamous cell carcinoma of the uterine cervix. A pilot study with intensification of dose

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Summary

Objective: This study included patients with inoperable primary or recurrent cervical cancer whose treatment plan called for exclusive radiotherapy. The endopoints of the study were to confirm the feasibility of concurrent radiotherapy and paclitaxel in relation to potential acute toxicity and to evaluate if an increase of complete local control might be obtained with the association of paclitaxel to radiotherapy as a radiosensitizer.

Methods: Twenty patients (13 new cases, stage IIB-III, and 7 with pelvic recurrences) were enrolled and, with exclusion of one recurrence, 19 were evaluable for acute toxicity and response. In new cases, radiotherapy was conventionally administered: 50.4 Gy/28 fractions by external beam (whole pelvis) followed by intracavitary cesium or reduced transcutaneous field. In recurrences, radiotherapy was performed with external beam only through individualized fields. Paclitaxel was administered weekly at the dose of 40 mg/m^2 or 60 mg/m^2 during the entire course of external radiotherapy.

Results: Complete regression (CR) as defined by clinical and imaging examinations was achieved in eight of the 13 new cases (62%) and in four of the six recurrences (66%), for a total complete response rate equal to 63%. Five patients (3 treated with 40 mg/m^2 and 2 with 60 mg/m^2) experienced grade 3 small bowel toxicity, one patient treated with 40 mg/m^2 grade 3 bladder toxicity and one patient treated with 60 mg/m^2 had grade 4 mucositis. Out of 12 CR patients at the end of treatment, ten maintain complete local remission for a median follow-up of 47 months but two have developed distant metastases.

Conclusion: The results confirm that this approach is feasible and suggest the use of paclitaxel as radiosensitizer in locally advanced cervical cancer.

Key words: Paclitaxel; Radiosensitizer; Cervical cancer.

Introduction

The rationale for concomitant chemotherapy and radiotherapy is based on the use of drugs which, in addition to a direct cytotoxic effect show the theoretical advantage to sensitize malignant tissue to the effect of radiation. These drugs include 5-fluorouracil, cisplatin and more recently paclitaxel.

In vitro studies on a human leukemic cell line (HL-60) [1] showed that taxol is likely to have a radiosensitizing effect due to its capability to block dividing cells in the G2-M phase of the cell cycle. Recent unpublished data of the Istituto Nazionale Tumori of Milan [2] on a non-small cell lung cancer cell line focused on interaction when the cells were exposed to paclitaxel 24 hours before radiation. This time-dependence had already been shown in radiobiological studies performed at Columbia University [3]: the time-dependence appeared to be related to the accumulation of paclitaxel-treated cells in the radiosensitive G2 and M phases of the cell cycle. The greatest effect of radiation and paclitaxel was seen at 24 hours, corresponding to a population in which nearly all cells had a G2/M DNA content. In some tumor cell lines a significant benefit from the combined treatment of paclitaxel plus radiation was shown [4, 5]: radiosensitization activity was noticed in human astrocytoma, human breast carcinoma, and human melanoma cell lines. In cervical carcinoma cell lines, like ME180 and SiHa, paclitaxel increased radiation toxicity and the interaction was found to be supraadditive [6] while an additive interaction was shown in cervical cell lines HTB-31 or HTB-35 [7]. On the contrary, no radiosensitization effect was reported in other human cervical carcinoma cell lines like C-33A and MS751 [8].

In different sites, such as head and neck, lung, breast and brain tumors paclitaxel has been combined with radiation in phase I clinical studies [3, 9, 10]. In a phase II study on non-small cell lung cancer [11] the maximum tolerated dose was 60 mg/m^2/week; in these series an overall response rate (complete plus partial) was achieved in 84% of patients. Other studies demonstrated that combination paclitaxel/cisplatin [12] or paclitaxel/cispla-

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tin and etoposide [13] in association with radiotherapy was a promising treatment for stage III non-small cell lung cancer.

In locally advanced cervical cancer, two phase I studies about combination paclitaxel/cisplatin with radiotherapy have been published [14, 15]. Both studies in which a dose escalation of weekly paclitaxel was used demonstrated that up to 50 mg/m^2/week of paclitaxel is well tolerated when associated to cisplatin in patients undergoing pelvic radiation therapy.

The present study included only those patients with bulky, inoperable, locally advanced stages or postsurgical local recurrences of uterine cervix cancer whose treatment plan called for conventional radiotherapy. Besides confirming the feasibility of concurrent radiotherapy with paclitaxel as a radionsensitizer in relation to potential acute toxicity, the endopoint of the study was to evaluate if an increase of local response rate can be obtained with the association.

Materials and Methods

Twenty patients with histologically proven squamous cell carcinoma of the uterine cervix were recruited. Of these, 13 were new cases, six had local recurrences after radical hysterectomy and one had persistent bulky disease after non-radical surgery; for analytical purposes, the last was considered among the recurrences. With exclusion of one case of recurrence not evaluable, 19 patients were evaluable. The 13 new cases included nine patients with FIGO stage IIIB [16] and four patients with stage IIB. Of the six recurrences, five patients had relapse in the lateral pelvis, one of which had previously been postoperatively irradiated with external beam and endovaginal brachytherapy at the vaginal cuff; and one showed bulky parametrial residual disease following non-radical surgery on the primary tumor, as mentioned above. The median age of the patients was 56 years (range: 38-69). The criteria for eligibility and the pretreatment evaluations are reported in Table 1. Informed consent was given by all the patients.

The treatment protocol schedule consisted of a course of radiotherapy combined with concomitant paclitaxel administered on the first or second day of each week during the entire course of transcutaneous treatment. Paclitaxel was diluted in 1000 ml of normal saline and administered by 3-hour continuous infusion. Prednisone 25 mg po was administered 12 hours before and premedication consisted of hydrocortisone 250 mg iv bolus, cimetidine 300 mg iv bolus and chlorphenamine 10 mg im, 30 minutes before paclitaxel. In the first 13 cases paclitaxel was administered at a dose of 40 mg/m^2, in the further six cases the dose was increased to 60 mg/m^2.

Radiotherapy was administered conventionally: all new cases received primary irradiation to the whole pelvis (planning target volume - PTV-1) with two opposed large diamond-shaped pelvic fields A-P and P-A of up to 50.4 Gy/28 fractions, one fraction per day, five days per week. In the 13 new cases the external beam irradiation to PTV1 was followed by one intracavitary cesium insertion in seven cases, and by transcutaneous fields in the other six patients: the modality of the boost dose (PTV2) was selected according to external pelvic radiation response and clinical feasibility of brachytherapy. The boost dose to PTV2 ranged from 13 to 15 Gy. The dose to the whole pelvis was defined at the isocenter (ICRU point) [17]. The cumulative target dose (whole pelvis plus boost) was calculated as the minimum target dose, i.e. at the boundary of the PTV2, both with brachytherapy and external beams. In the recurrences, following the whole pelvis radiation treatment, the boost dose was always administered with external beams, usually through individualized arrangements: multiportal technique, moving beam, or both were used in order to reach a total minimum target dose to PTV2 ranging from 63 to 65 Gy. Only in one case with recurrence was the radiation technique different: the treatment started with a multiportal technique on a small pelvic volume because the patient had previously been submitted to adjuvant radiotherapy (small pelvic field plus endocavitary vaginal boost with cesium) after surgery.

According to the length of the transcutaneous radiation therapy, the number of concomitant weekly courses of paclitaxel was planned to be between five and seven. All patients were evaluable for response and acute toxicity. Response was evaluated three months after the end of radiotherapy by means of a clinical examination and computed tomography (CT) and/or magnetic resonance (MR). Complete regression (CR) was defined as the disappearance of the disease according both to clinical and radiological examinations. Partial regression (PR) was defined as a tumor size reduction of more than 50%. A regression of less than 50% or stable disease was defined as no change (NC). Acute hematological toxicity was monitored weekly during treatment through serum examination and blood cell counts. Every two weeks a cardiological evaluation was performed. All patient symptoms (e.g. diarrhea, vomiting, dysuria) were reported. Toxicity was scored according to the WHO criteria [18]. Data analysis was performed in December 2000.

Results

All patients completed the planned course of radiotherapy. All but one received five to seven weekly cycles of paclitaxel (five patients received seven courses, six patients six courses, and seven patients five courses; in one case treated with 40 mg/m^2 the administration of paclitaxel was interrupted after three cycles due to acute small bowel toxicity).

In patients treated with 40 mg/m^2 of paclitaxel CR was achieved in three of the seven new cases and in four of the six recurrences. PR was observed in one of the seven

Table 1. — *Criteria for eligibility and pretreatment evaluation*

Criteria for eligibility
• New cases, stage IIB-IIIA-IIIB
• Postsurgical pelvic recurrence not amenable to surgery
• Normal cardiovascular function
• WBC > 3,000; HB > 10, PLTS > 120,000; Bilirubin < 2; Creatinine < 1.5
• Performance status < 1 (ECOG)
• Informed consent
Pretreatment evaluation
• Pelvic examination, without and with general anaesthesia
• Abdominopelvic imaging by CT or MR
• Cystoscopy
• Rectosigmoidoscopy
• Cardiovascular evaluation
• Chest X-ray
• Serological evaluation of liver and kidney functions
• Blood cell count

Table 2. — *Local response and outcome of 19 treated patients*

No. pts	Age (yrs)	Stage	Taxol dose mg/m²	Response	Outcome from the start of treatment (months)
1	68	IIIB	40	NC	PRO (5). DOD (7)
2	64	IIIB	40	NC	PRO (8). DOD (19)
3	66	IIIB	40	CR	CR. Alive NED (55)
4	40	IIIB	40	CR	CR. Alive NED (49)
5	38	IIIB	40	NC	PRO (9). DOD (10)
6	48	IIIB	40	PR	PRO (14). CT → CR DOD (37)
7	66	IIB	40	CR	CR M+ (21) → CT + RT → CR Alive NED (50)
8	45	Recurrence	40	NC	PRO (7). DOD (11)
9	40	Recurrence	40	CR	CR. Lost to follow-up NED (30)
10	62	Recurrence	40	CR	CR M+ (19) → CT Alive NED (51)
11	38	Recurrence	40	NC	PRO (4). DOD (7)
12	48	Persistent bulky disease	40	CR	CR. Alive NED (54)
13	69	Recurrence	40	CR	CR. Alive NED (45)
14	63	IIB	60	CR	CR. Alive NED (43)
15	42	IIIB	60	CR	Local relapse (11). DOD (17)
16	60	IIB	60	CR	CR. Alive NED (36)
17	68	IIB	60	CR	CR. Alive NED (34)
18	56	IIIB	60	CR	Local relapse, M+ (8). Alive NED (29)
19	54	IIIB	60	NC	PRO M+ (3). DOD (5)

NC: No change; CR: complete regression; PR: partial regression (≥50%); PRO: progression; DOD: dead of disease; NED: no evidence of disease; ED: evidence of disease; M+: metastases; CT: chemotherapy; RT: radiotherapy.

new cases. In five patients, three new cases and two recurrences, NC was observed. In this group with a median follow-up from the start of treatment of 37 months, all the seven patients who achieved CR are still in a local remission status and are alive, but two have developed distant metastasis. The PR patient treated with salvage chemotherapy for six cycles obtained CR but died of distant metastases. The five patients with NC at the end of the combined treatment developed fast local disease progression, and died in spite of salvage chemotherapy.

In the six cases treated with a dose of 60 mg/m² CR was obtained in five. With a median follow up of 31.5 months, three maintained CR and are alive, one developed local relapse and distant metastasis and is alive with evident disease, while one patient had local progression and died. The patient with NC had local progression, distant metastasis and died. Considering the different dosages of paclitaxel, CR was obtained in seven of the 13 patients treated with 40 mg/m² and in five of the six patients treated with 60 mg/m² of paclitaxel.

Cumulatively considered, CR was observed in eight of the 13 new cases (62%) and in four of the six recurrences (66%) (Table 2). Out of 12 CR patients at the end of combined treatment, ten have maintained complete local remission for a median follow-up of 47 months although two of those have developed distant metastases.

Severe adverse effects during treatment developed in seven patients. In the group treated with 40 mg/m² three patients experienced grade III small bowel toxicity and one patient grade III bladder toxicity (WHO parameters) [18]. In one case of small bowel toxicity the administration of paclitaxel was interrupted after three cycles, but the radiation treatment was not discontinued. In the group treated with 60 mg/m², two patients developed grade III small bowel toxicity and one patient grade 4 mucositis, all without treatment interruption.

Only moderate hematological toxicity was observed, never producing interruption of treatment. No cases of cardiac toxicity, alopecia, or neurotoxicity were recorded. In one case chronic proctitis appeared as a long-term toxicity.

Discussion

Definitive radiotherapy represents the standard treatment for locally advanced (FIGO stage IIB-III) or recurrent squamous cell carcinoma of the uterine cervix. Radiotherapy is usually performed applying a whole pelvis field with a dose of up to 50 Gy followed by a boost with endocavitary brachytherapy or external beam to reduced volume. Despite the large tumor doses conventionally administered (65 Gy or more), failures are not uncommon. According to Perez [19] the actuarial highest probability of locoregional control after radiotherapy alone is 60% for stage III. On the other hand, achie-

ving local CR after radiotherapy represents an important predictive factor of survival, being a 5-year survival rate of 76% when local CR is obtained, versus 41% when CR is not achieved [20]. The improvement of pelvic control cannot be reached by increasing the radiation dose beyond the current levels without prohibitive morbidity. The consequence, in recent years, has been the development of chemo-radiotherapy regimens with which favorable results have been reported in tumors of other sites.

Concurrent chemo-radiotherapy has theoretical advantages on radiotherapy alone. Chemotherapy in fact may act synergistically with radiotherapy inhibiting the repair of radiation-induced damage, promoting the synchronization of cells into a radiation-sensitive phase of the cycle, and reducing the fraction of hypoxic cells resistant to radiation. Furthermore chemotherapy may independently increase the rate of death of tumor cells. Nevertheless, since the doses of drugs administered concurrently with radiotherapy are inferior to those commonly used, it is not lilkely that such treatment will affect distant metastases [21].

In the last decade several series concerning the combination of radiotherapy with concomitant chemotherapy have been reported in locally advanced cervical cancer. Most of these phase II studies, consisting of the administration of two or three cycles of fuorouracil with or without mitomycin C [22-30], cisplatin or platinum containing regimen [31-35] during a conventional course of radiotherapy, showed that the integrated approach was effective with respect to local control, but no significant survival benefit has been proven.

Only recently three large phase III studies [36, 37, 38] on patients with locally advanced cervical cancer reported that the addition of chemotherapy with cisplatin and fluorouracil to external and intracavitary radiotherapy improved the survival rate, with a rate of both locoregional recurrences and distant metastases significantly higher in patients treated with radiotherapy alone.

Our pilot study shows that concurrent administration of paclitaxel at the weekly dose of 40-60 mg/m^2 and radiotherapy with conventional fractionation is feasible. The acute toxicity is not increased in respect to what is commonly observed during a conventional course of exclusive radiation treatment. It is worth stressing that no particular efforts, i.e. technical devices, were used in order to avoid irradiation of the small bowel. A complete response rate of 63% and ten local CR maintained for a median follow-up of 47 months, can be considered as a satisfactory local result, bearing in mind that one-third of the patients had pelvic recurrences. In conclusion paclitaxel may be considered an effective radiosensitizer drug.

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