Concomitant chemobrachyradiotherapy with ifosfamide and cisplatin followed by consolidation chemotherapy in the treatment of locally advanced adenocarcinoma or adenosquamous carcinoma of the cervix uteri

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Summary

The optimal treatment of women with locally advanced adenocarcinoma or adenosquamous carcinoma of the cervix uteri is still undefined.

We report a series of four consecutive patients with locally advanced adeno- or adenosquamous carcinomas of the uterine cervix (FIGO Stages IB-IIIB) treated by concomitant chemobrachyradiotherapy with ifosfamide and cisplatin followed by one to four cycles of consolidation chemotherapy with the same drug combination. After completion of this treatment all patients showed complete clinical remission. Now, after a median follow-up of 40 (range: 13.5-61) months all patients still present with no evidence of disease.

Despite the low number of patients in this series we may conclude that concomitant chemobrachyradiotherapy with ifosfamide and cisplatin followed by consolidation chemotherapy with the same drug combination is an efficacious treatment of patients with locally advanced adeno- or adenosquamous carcinomas of the cervix uteri.

Key words: Concomitant chemoradiation; Ifosfamide; Cisplatin; Consolidation chemotherapy; Adenocarcinoma of the cervix uteri; Adenosquamous carcinoma of the cervix uteri.

Introduction

Cervical cancer is one of the most common cancers among women worldwide with its highest incidence in developing countries [1]. Despite effective screening programs cervical carcinomas are still very often diagnosed only in advanced stages, i.e. FIGO-IB2 (bulky) to IVA. Over 90% of cervical cancers are squamous cell carcinomas [2]. Approximately 7%-10% are adenocarcinomas, 2%-5% are adenosquamous carcinomas and 1%-2% are clear cell carcinomas, mesonephric type [2]. Currently, the standard therapeutic approach for all patients with advanced stage carcinoma, regardless of the histologic cell type, is cisplatin-based concomitant chemoradiotherapy, although this treatment is based on data, which were generated exclusively on patients with squamous cell carcinoma [3]. Thus, the assumption that this approach will also be efficacious in the treatment of adeno- or adenosquamous carcinomas of the cervix uteri is only based on indirect evidence. Moreover, there is some evidence that adeno- and adenosquamous carcinomas have higher local recurrence rates compared to squamous cell carcinoma when treated with radiation therapy [4]. Furthermore, the 5-year survival rates of patients with adenosquamous carcinoma are worse than those of patients with adenocarcinoma of the uterine cervix [5, 6].

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Materials and methods

In this case series all consecutive patients with adeno- or adenosquamous carcinomas of the cervix uteri admitted to the Center of Oncology at the Clinical Hospital Split between January 1, 1999 and December 31, 2003 were enrolled. The patients with adeno- or adenosquamous carcinomas underwent the same treatment as those with squamous cell carcinomas, i.e. concomitant chemobrachyradiotherapy with ifosfamide and cisplatin followed by consolidation chemotherapy with the same drug combination, a novel treatment modality that has previously been shown to be highly efficacious [7].

External radiation was applied as a combination of the 4-field box technique and anterio-posterior/posterio-anterior (AP-PA) field technique. All patients received 25 fractions of external radiotherapy with a daily dose of 200 cGy. After completion of 15 Gy of external radiotherapy, the first low-dose-rate brachyradiotherapy insertion with a dose of 30 Gy was performed. The second insertion was scheduled three weeks apart from the first one, after a total dose of 45 Gy. Both brachyradiotherapy applications were performed with a low-dose-rate ^{137}Cs machine with a dose rate of 1.5 cGy per minute. After application of 25 Gy by means of external radiotherapy, an individually made central block was implemented to protect over-irradiation of the central pelvic tissues. Altogether, a total dose of 85 Gy of irradiation was applied to point A by means of external radiotherapy (25Gy) and brachyradiotherapy (60Gy). Concomitantly with the two intracavitary brachyradiotherapy insertions, 2 cycles of chemotherapy with ifosfamide at a dose of 2000 mg/m^2 per 24-hour infusion and cisplatin at a dose of 75 mg/m^2 per 1-hour infusion, respectively, were administered. After the concomitant chemobrachyradiotherapy, the patients were scheduled to

receive four courses of consolidation chemotherapy, every three weeks consisting of cisplatin 75 mg/m² on day one [1-hr infusion) and ifosfamide 2000 mg/m² (3-hr infusion) on three consecutive days.

The following staging diagnostic procedures were performed on all patients: gynaecological examination, chest X-ray, CT scan of abdomen and pelvis, and intravenous pyelography. Standard blood haematology and biochemistry tests were performed including a creatinine clearance test. All patients had to have a creatinine clearance above 50 ml/min which was the lower limit for the administration of the before-mentioned chemotherapy regimen.

Clinical response was evaluated by means of gynaecological examination with cervical punch biopsy and CT-scan of the abdomen and pelvis. This reevaluation was performed after application of the third chemotherapy cycle, i.e. after the first cycle of consolidation chemotherapy.

After the end of the treatment the patients were regularly followed up by gynaecological, radiological (CT-scan of the abdomen and pelvis, abdominal ultrasound, chest X-ray) and laboratory (blood haematology and biochemistry tests) examinations.

Results

Between January 1, 1999 and December 31, 2003 four consecutive patients with adeno- (No. = 3) or adenosquamous (No. =1) carcinomas were treated at the Center of Oncology, Clinical Hospital Split. All patients but one were postmenopausal at the time of their initial diagnosis; the FIGO Stages were IB1, IB2 (bulky), IIB and IIIB, respectively (Table 1).

All patients received the full dosage of radiotherapy plus concomitantly two cycles of chemotherapy with cisplatin and ifosfamide and at least one cycle of consolidation chemotherapy, as described before. Due to haematologic toxicities of grade 3 occurring after the first (cases III and IV) or second (case I) cycle of consolidation chemotherapy, further chemotherapy cycles had to be cancelled; only one patient (case II) received all four cycles of consolidation chemotherapy as scheduled. None theless, all patients showed no evidence of disease at a median follow-up of 40 months (range 13.5-61 months) after their initial diagnosis.

Discussion

Despite the advances in the management of locally advanced cervical carcinoma with surgery or concomitant chemoradiotherapy the optimal management for adenocarcinoma and adenosquamous carcinoma has not yet been defined.

For squamous cell carcinoma of the cervix cisplatin has been the most active single agent with response rates ranging between 20% and 30% [8]. Ifosfamide is the second most active single agent with response rates of up to 22% [9]. The combination of ifosfamide-cisplatin (IC) yielded significantly higher response rates and longer progression-free survival than either cisplatin alone or the combination of cisplatin and mitolactol [10]. These findings led to the use of the IC protocol as one of the standard regimens for the treatment of metastatic squamous cell cervical cancer.

Radiotherapy can be delivered in three schedules: sequentially, alternating, and concomitantly. The concomitant approach has the advantage of not delaying a potentially curative therapy, i.e. radiotherapy. This strategy also minimises the risk that cross-resistant tumour cells develop. On the other hand, the concomitant chemoradiotherapy approach shows the most severe toxicity. A significant survival benefit of 30% to 50% was achieved when cisplatin-based chemotherapy was administered concurrently with radiation therapy [11-15].

Tonkin *et al.* described a synergistic action between ifosfamide and low-dose-rate radiotherapy [9]. When ifosfamide was applied during low-dose irradiation it enhanced radiation cell killing to a large extent. Based on these experimental findings we introduced a new approach for the treatment of advanced squamous cell cervical carcinoma – concomitant chemobrachyradiotherapy (low-dose-rate) with ifosfamide and cisplatin [7]. With this treatment, overall and disease-free survival rates were 91% and 87%, respectively, after a median follow-up of 36 months [7]. The additional benefit of so-called consolidation or adjuvant chemotherapy – as in our treatment schedule for patients with locally advanced cervical cancer – has recently been published [16-18]. Moreover, there are positive examples for the value of adjuvant chemotherapy in the treatment of initially more chemoresistant tumours, i.e. colon and lung cancer [19-21].

Table 1. — *Characteristics and outcome of four consecutive patients with locally advanced adeno- or adenosquamous cervical carcinomas treated with concomitant chemobrachyradiotherapy followed by consolidation chemotherapy with cisplatin/ifosfamide.*

Case No.	Initial diagnosis (month/year)	Age at initial diagnosis (years)	Histologic type	FIGO stage	Concomitant chemobrachy-radiotherapy	Consolidation chemotherapy	Status (months after initial diagnosis)	Comments
I	07/99	64	Adeno-ca Grade 2	IB1	complete	2 cycles	No evidence of disease	leukopenia II° anemia III°
II	11/00	61	Adeno-ca Grade 2	IIIB	complete	complete (4 cycles)	NED (35+)	anemia II° leukopenia III°
III	01/01	65	Adeno-ca Grade 1	IIB	complete	1 cycle	NED (45+)	anemia I° leukopenia III° (> 3 weeks)
IV	08/03	37	Adenosquamous-ca Grade 2	IB2-	complete	1 cycle	NED (13.5+)	leukopenia II° anemia III°

Based on the before-mentioned very promising results yielded with the concomitant chemobrachyradiotherapy with ifosfamide and cisplatin followed by consolidation chemotherapy with the same drug combination in patients with locally advanced squamous cell carcinoma of the uterine cervix we applied the same protocol in four consecutive, i.e. non- selected, patients with locally advanced adeno- or adenosquamous cervical carcinomas. All patients showed a complete clinical response proven histologically by punch biopsies and after a median follow-up of 40 (range 13.5-61) months after initial diagnosis all patients were without any evidence of disease.

The reported higher local failure rates in patients with adeno- or adenosquamous carcinomas compared with patients with squamous cell carcinoma [4] as well as higher incidence of distant metastases in patients with adenocarcinoma [22] justify our treatment approach even more.

In conclusion, we believe that patients with locally advanced non-squamous cell carcinoma, i.e. adeno- or adenosqamous carcinomas, should be treated as aggressively as possible, combining both modalities, i.e. radiotherapy and chemotherapy. The very promising results in our admittedly rather small series nevertheless warrant the testing of this treatment strategy in a larger series of patients in order to improve the treatment of patients with cervical adeno- or adenosquamous carcinomas and in order to increase our knowledge on these subentities of cervical carcinomas.

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