Pattern of Failures and Clinical Outcome of Patients with Locally Advanced Cervical Cancer Treated with a Tailored Integrated Therapeutic Approach

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Abstract. Aim: To review a tailored treatment with concurrent chemoradiotherapy (CT/RT) or neoadjuvant chemotherapy (NACT) followed by radical hysterectomy in locally advanced cervical cancer. Patients and Methods: One hundred and four patients were treated with a tailored therapeutic approach. CT/RT was the standard treatment for patients with stage Ib2-IIb disease aged more than 70 years, or with high surgical risk, as well as for those with stage III-IV disease. NACT followed by radical hysterectomy was the treatment of choice for patients with stage Ib2-IIb disease, maximum age of 70 years and good performance status. Results: For the 61 women who underwent CT/RT, 5-year disease-free (DFS) survival and 5-year overall survival (OS) were 62% and 71%, respectively. Patient outcome was associated with the clinical response to CT/RT (complete responders versus others: 5-year DFS, 81% versus 19%, p<0.001; 5-year OS, 84% versus 37%, p=0.001). For the 43 women who underwent NACT, 5-year DFS and 5-year OS were 66% and 75%, respectively. Patient outcome was associated with the pathological response to chemotherapy (optimal responders versus others: 5-year DFS, 89% versus 62%, p=0.03; 5-year OS, 90% versus 72%, p=0.05). Conclusion: Tailored treatments obtained satisfactory clinical outcomes in locally advanced cervical cancer. Optimal pathological response to NACT has been found to be a surrogate endpoint of OS. The identification of biological variables able to predict response to NACT is strongly warranted for an accurate selection of patients who may really benefit from chemosurgical treatment.

Radical radiotherapy, consisting of external pelvic beam irradiation and brachytherapy, has long been the treatment of choice for locally advanced cervical cancer. Concurrent cisplatin-based chemoradiotherapy is currently accepted as the new standard of care. Five prospective randomised trials showed a significant improvement of the clinical outcome for patients who received this combined treatment compared with those who received radiotherapy alone (1-7). A meta-analysis of 13 randomised clinical trials revealed that concurrent chemoradiotherapy obtained a 6% improvement in 5-year survival [hazard ratio (HR)=0.81, 95% confidence interval (CI)=0.71-0.91, p=0.0006] with respect to radiotherapy alone (8). Neoadjuvant chemotherapy followed by radical surgery appears to be an interesting alternative therapeutic option, at least for patients with stage Ib2-IIb disease (9-14). A meta-analysis assessed six randomised trials comparing neoadjuvant chemotherapy and surgery versus surgery in women with early or locally advanced cervical cancer (11). Exploratory analyses of pathological responses showed a significant decrease in adverse pathological findings with neoadjuvant chemotherapy [odds ratio (OR)=0.54, 95% CI=0.39-0.73, p<0.0001 for lymph node status and OR=0.58, 95% CI=0.41-0.82, p=0.002 for parametrial infiltration].

The aim of the present retrospective investigation was to assess the pattern of failures and the clinical outcome of patients with locally advanced cervical cancer treated with a tailored integrated therapy.

Patients and Methods

The present study retrospectively assessed 104 patients with locally advanced cervical cancer referred to the multidisciplinary Committee of Gynaecologic Oncology of the Pisa University Hospital between 1999 and 2009, and treated with either exclusive concurrent chemoradiotherapy or neoadjuvant chemotherapy followed by radical hysterectomy. Patients with poor performance status treated with radiotherapy alone were not included in this analysis.
The hospital records of each patient were reviewed. Pretreatment evaluation included clinical history, physical assessment, vaginal-pelvic examination, colposcopy, biopsy, complete blood analysis, chest X-rays and abdominal-pelvic computed tomography (CT) scan. Cytoscopy and/or proctoscopy were performed if there was clinical or CT suspicion of bladder or rectal involvement. Further investigations [namely magnetic resonance imaging (MRI) scan, intravenous pyelography, transvaginal and/or transrectal ultrasound] were performed when deemed appropriate. All patients were initially evaluated by a gynaecologist and a radiation oncologist sharing the decision-making for every single case.

Tumours were staged according to the International Federation of Gynecology and Obstetrics (FIGO) criteria (15).

Exclusive concurrent chemoradiotherapy was the standard treatment for patients with stage Ib2-IIb cervical cancer aged more than 70 years or with high surgical risk, as well as for those with stage III-IV disease regardless of age. Neoadjuvant chemotherapy followed by radical hysterectomy and pelvic lymphadenectomy was the treatment of choice for patients with stage Ib2-IIb cervical cancer, maximum age of 70 years and good performance status.

Regarding chemoradiotherapy, external beam irradiation was performed with a 15 MV beam and with a four-field conformal technique (gantry angles at 0˚, 90˚, 180˚ and 270˚). A 50.4-54 Gy dose was given in daily fractions of 1.8 Gy. The pelvic target volume was outlined on a CT scan. When common iliac or para-aortic lymph node involvement was detected on the CT scan, the para-aortic space was included into the planned volume (45 Gy). A concurrent cisplatin-based chemotherapy was added to the external pelvic beam irradiation. Subsequently, a high-dose rate (HDR) brachytherapy was delivered as a boost with a three-way Fletcher-Williamson applicator set (Nucletron B.V., Veenendaal, Netherlands). The treatment plan was performed on a CT scan with the Nucletron Brachyvision v14.2 treatment planning system (Nucletron B.V., Veenendaal, the Netherlands). The prescribed dose to the high-risk target volume was 20-25 Gy in 5-7 Gy fractions. Rectal and bladder doses were estimated from dose volume histograms on CT-based plans and were evaluated to the dose points specified by the International Commission on Radiation Units and Measurements (16).

Response to chemoradiotherapy was assessed by vaginal-pelvic examination, colposcopy and CT scan, two months after the treatment completion. MRI was routinely used after 2005. Responses were evaluated as follows: i) complete response; disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) were reduced in the short axis to less than 10 mm; ii) partial response: at least a 30% decrease in the sum of diameters of target lesions, using the baseline diameter sum as reference; iii) progressive disease: at least a 20% increase in the sum of diameters of target lesions. The appearance of one or more new lesions was also considered progression; iv) stable disease: insufficient shrinkage to qualify for partial response or insufficient increase to qualify for progressive disease (17).

Regarding neoadjuvant chemotherapy, various cisplatin-based regimens were used over time and the clinical responses were evaluated 3-4 weeks after chemotherapy with vaginal-pelvic examination, colposcopy and CT scan and, in selected cases, MRI. Radical hysterectomy with pelvic lymphadenectomy was performed within 2 weeks from re-evaluation. Pathological responses were retrospectively assessed according to the criteria suggested by Buda et al. (12). Complete response was defined as the complete disappearance of tumour in the cervix and paracervical tissues with negative lymph nodes. Optimal partial response was defined as persistent residual disease with less than 3 mm stromal invasion including in situ carcinoma on the surgical specimen. Suboptimal response was defined as persistent residual disease with more than 3 mm stromal invasion on the surgical specimen. Postoperative management was individually tailored on the basis of histopathological findings on surgical specimens, patient age and general conditions, after an extensive discussion with the patient.

All patients were periodically followed-up with clinical and radiological examinations until they died or until January 2010. The median follow-up period of survivors was 46 months (range, 13-119 months). The time from the start of concurrent chemoradiotherapy or from the first cycle of neoadjuvant chemotherapy to the detection of recurrence was defined as disease-free survival. The time from the start of concurrent chemoradiotherapy or from the first cycle of neoadjuvant chemotherapy to death or last observation was defined as overall survival.

The statistical package SAS, release 6.7 (SAS Institute Inc. Cary, North Caroline, USA) was used for computations. The cumulative probability of survival was estimated by the product-limit method. The log-rank test was used to compare the homogeneity of survival functions across strata defined by categories of prognostic variables.

Results

The general characteristics of patients with locally advanced cervical cancer are summarised in Table I. Some of the patients who received chemosurgical treatment were included in a previous paper (18).

Concurrent chemotherapy consisted of weekly cisplatin 40 mg/m² in 29 patients, weekly cisplatin 40 mg/m² plus weekly paclitaxel 30 mg/m² in 27 patients and other cisplatin-based combination in 5 patients. Clinical and radiological re-evaluation two months after the end of treatment showed a complete response in 53 (86.9%) patients, a partial response in 4 (6.6%) patients, a stable disease in 3 (4.9%) patients, and a progressive disease in 1 (1.6%) patient.

Regarding chemosurgical treatment, neoadjuvant chemotherapy consisted of: ifosfamide 5 g/m² (plus mesna 5 g/m²) 24-h continuous infusion on day 1 plus paclitaxel 175 mg/m² on day 2 plus cisplatin 75 mg/m² on day 2 (every 3 weeks for 3 cycles) in 26 patients; paclitaxel 175 mg/m² plus cisplatin 75 mg/m² (every 3 weeks for 3 cycles) in 12 patients; other cisplatin-based combination chemotherapy in 5 patients. The histopathological examination of surgical specimens showed a complete response in 7 (16.3%) patients and an optimal partial response in 5 (11.6%) patients, with an optimal pathological response rate of 27.9%. Twenty-eight (65.1%) patients had suboptimal response and 3 (7.0%) patients had stable disease. After surgery, 16 patients received additional cycles of chemotherapy with the induction regimen, 17 patients underwent concurrent chemoradiotherapy or radiotherapy alone, and 10 patients had no further treatment.

Of the 61 women who underwent chemoradiotherapy, 14 (22.9%) patients had recurrent tumours and 13 (21.3%) of them died as a result. The sites of recurrent disease are
shown in Table II. One patient with central pelvic recurrence underwent exenteration followed by chemotherapy and died 31 months later because of lung metastases. One patient with para-aortic relapse received chemoradiotherapy and is still alive and disease-free after 79 months from recurrence. Two patients with pelvic failure, 3 patients with pelvic plus extrapelvic recurrence, and 2 patients with extrapelvic failures underwent chemotherapy and died within 6-18 months. The other 5 patients with recurrent disease received no further treatment and died within 2-12 months.

The 5-year disease-free survival and 5-year overall survival were 62% and 71%, respectively. The log-rank test showed that the 5-year disease-free survival and the 5-year overall survival were significantly associated with the response to chemoradiotherapy (5-year disease-free survival: 81% complete versus 19% other, p<0.001, and 5-year overall survival: 84% complete versus 37% other, p=0.001), but not with FIGO stage (Ib2-IIa versus IIb-IV), patient age and concurrent chemotherapy regimen (paclitaxel–platinum-based chemotherapy versus platinum-based chemotherapy without paclitaxel) (data not shown).

Moderate to severe late adverse effects occurred in 6 (9.8%) women. Two patients experienced ureteral stenosis, 2 patients had grade 2-3 proctitis, 1 patient had grade 3 haemorrhagic cystitis, and 1 patient had rectal stenosis. No treatment-related death occurred.

Of the 43 women who underwent neoadjuvant chemotherapy and radical hysterectomy, 11 (25.6%) patients developed recurrent tumours, 8 (18.6%) patients died of the tumour and 1 (2.3%) patient died of intercurrent disease with no clinical evidence of tumour. The sites of recurrent disease are reported in Table II.

Discussion

Concurrent cisplatin-based chemotherapy and external pelvic beam irradiation plus brachytherapy is generally regarded as the standard treatment for locally advanced cervical cancer (1-8). However, neoadjuvant chemotherapy...
followed by radical hysterectomy is able to obtain satisfactory results in patients with stage Ib2-IIb cervical cancer but not in those with more advanced disease (9-14). A European Organization for Research and Treatment of Cancer (EORTC) randomised trial is currently comparing chemosurgical treatment versus concurrent chemoradiotherapy in patients with FIGO Ib2, Ia > 4 cm or IIb cervical cancer (EORTC protocol 55994). In the present study, the results of a tailored integrated therapeutic approach are assessed retrospectively in women with locally advanced disease evaluated collegially by a gynaecologist and a radiation oncologist who share the decision-making for every single case. Treatment modality was chosen taking into consideration both tumour stage and patient characteristics. Patients with stage III-IV disease received exclusive chemoradiotherapy regardless of age, whereas patients with stage Ib2-IIb underwent neoadjuvant chemotherapy followed by radical hysterectomy, if they had a maximum age of 70 years and they were in good general condition, or exclusive chemoradiotherapy, if they were aged more than 70 years or if they had high surgical risk.

Morris et al. (1), Whitney et al. (3) and Rose et al. (7) reported that chemoradiation obtained a 5-year overall survival ranging from 60% to 73% in patients with stage Ib-IIV cervical cancer. In the study of Benedetti-Panici et al. (10), neoadjuvant chemotherapy and radical surgery achieved a 5-year overall survival of 65% in patients with FIGO stage Ib2–IIb disease. Therefore the results obtained in the present study compare favourably with those reported in the literature for both chemoradiotherapy and neoadjuvant chemotherapy plus surgery, which appears to support the treatment strategy. Optimal pathological response to neoadjuvant chemotherapy has been confirmed to be a surrogate endpoint of survival in agreement with the literature (12, 19-21). Therefore the identification of biological variables able to predict response to neoadjuvant chemotherapy is strongly warranted for an accurate selection of patients who may really benefit from chemosurgical treatment. Patients with pretreatment and biological findings suggestive of a low chance of optimal response to chemotherapy should be treated with exclusive chemoradiotherapy.

References


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