Efficacy of cisplatin and cyclophosphamide combination for recurrent and metastatic carcinoma of the uterine cervix

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Summary

The efficacy of a combination of cyclophosphamide and cisplatin in patients with metastatic and recurrent carcinoma of the cervix, was tested.

Thirty patients were included in the study. Initially, 27 patients (90%) had received pelvic radiation and intracavitary boost and one patient was additionally given paraaortic radiation. Cisplatin was given at 75 mg/m^2 followed by cyclophosphamide at 750 mg/m^2 on day 1 with three weekly intervals for a maximum of six cycles. All patients received a median of four cycles of chemotherapy.

The overall response rate for all eligible patients was 20% (continuous CR: 1, CR: 1, PR: 4 patients). Overall response rate and progressive response in patients with relapse within the previous radiation field were 9.5% and 66.7%, respectively; while for patients who had recurrent disease outside any irradiated area both were 44.4%. Eighteen patients (60%) had early withdrawal from the planned schedule, which was due to patient incompliance in seven patients (23.3%), disease progression in ten (33.3%) and early death after the first cycle in one patient (3.3%). Anemia was the most frequent toxicity, necessiating 24 transfusions in nine patients (30%). WHO grade 3 and 4 toxicity were anemia: 13 (43.3%), leucopenia: one (3.3%), thrombocytopenia: two (6.6%), renal: one, emesis: nine (30.0%) patients. The median survival duration for all eligible patients was 11 months. Univariate analysis revealed that progressive response to chemotherapy was the only prognostic factor for survival (7.1 vs 16.8 months, p = 0.003).

The combination of cisplatin and cyclophosphamide did not appear to be more active than single agent cisplatin in this patient group with a relatively poor prognosis. Further studies are required to determine a better therapeutic approach for patients with relapsed carcinoma of the cervix.

Key words: Recurrent carcinoma of the uterine cervix; Chemotherapy; Cisplatin; Cyclophosphamide.

Introduction

Carcinoma of the uterine cervix is one of the leading malignant disesases among women. At earlier stages radiation therapy or surgery yields survival rates ranging between 75 to 90% at five years. However, there has been no satisfactory response with any type of treatment modality for patients with metastatic and recurrent disease; rendering cervical carcinoma as a significant cause of mortality and poor quality of life at advanced stages. In selected cases with low tumor burden, radiotherapy or surgery may result in prolonged survival rates reaching 10% to 30% [1]. Nevertheless, this favorable outcome can only be achieved in a minority of cases. Therefore, chemotherapy remains as a useful option for patients who present with advanced disease that is not curable by surgery or radiation treatment.

Single agent therapies often yield response rates ranging from 20 to 30%, with a median response duration of three to six months and a median survival of five to nine months [1, 2]. Cisplatin is by far considered as the single most active agent for cervical cancer and there are numerous trials in the literature that have tested its efficacy against combinations [2]. Despite higher response rates and prolonged progression-free survival in some, these trials have failed to show a superiority of combinations against single-agent therapy and cisplatin has gained wide acceptance as the standard treatment regimen for metastatic and recurrent cervical carcinoma [3-5]. However, the poor outcome in those patients justifies the continuous search for different combinations that would not only yield better response rates and survival, but also improve the quality of life.

Although triple and quadruple combinations of cyclophosphamide with cisplatinum and agents such as bleomycin and doxorubicin were commonly employed regimens in studies dating back to the 1980's; owing to modest response rates and substantial toxicity generated with multi-agent therapies, there has been a tendency for dual combinations of cisplatinum including ifosfamide or newer generation agents instead of cyclophosphamide in the past decade [6, 7]. Ifosfamide has already been proved to be an active agent for cervical carcinoma resulting in response rates ranging between 11 to 50% [8,9]. Nevertheless, the high incidence of toxicity has precluded its widespread use. In order to reproduce the beneficial effect of cisplatinum combined with an alkylating agent without the cost of significant toxicity, we replaced ifosfamide with cyclophosphamide and evaluated the influence of response to a combination regimen including cisplatinum and cyclophosphamide on survival in our patients with metastatic and recurrent carcinoma of the uterine cervix.

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Patients and Methods

Thirty patients who were referred to the medical oncology unit with metastatic and recurrent cervical carcinoma between 1991 and 1999 were included in the protocol. All patients underwent a complete physical and gynecologic examination before the study treatment. Initial laboratory work up included complete blood count, biochemistry, electrocardiogram, conventional chest X-ray, CT-scan or MRI of the abdominopelvic region. If required, a thoracic CT-scan was also planned. All patients who had given consent and with a WHO performance status of 0-2, in addition to adequate renal, hepatic, cardiac functions and bone marrow reserve were considered eligible for the study treatment. Patient characteristics are listed in Table 1.

At the time of initial diagnosis, 27 patients (90%) had received pelvic radiation treatment at a dose of 50 Gy, followed by an intracavitary boost at 20 Gy given at 180 cGy fractions. One patient had been additionally given primary radiation to the paraaortic area. Four patients (13.3%) had a radical hysterectomy operation at initial diagnosis.

Table 1. — *Patient characteristics.*

	n	%
Age-median (range)	*50 (32-70)*	
Menopausal staus		
Premenopausal	12	40
Postmenopausal	16	53.3
Unknown	2	6.7
Histology type		
Squamous carcinoma	27	90
Adenosquamous carcinoma	1	3.3
Adenocarcinoma	2	6.7
Stage at initial diagnosis		
Ib	2	6.7
II	14	46.6
III	11	36.6
IV	3	10.0
Previous treatment		
Radiotherapy	25	83.3
Surgery	3	10.0
Surgery+adjuvant radiotherapy	2	6.7
Site of recurrent tumor		
Inside irradiated field	21	70.0
Outside irradiated field	6	20.0
Inside+outside irrdiated field	3	10.0

Treatment schedule:

Cisplatin was given at 75 mg/m^2 as a 2-hour IV infusion with adequate hydration, followed by cyclophosphamide given as a short IV infusion at 750 mg/m^2 on the first day with three weekly intervals for a maximum of six cycles. Cycles were delayed if these criteria were encountered on the day of the planned cycle: neutrophil count less than 2 x 10^9/l, platelet count less than 100 x 10^9/l, or presence of grade 3-4 non-hematologic toxicity in the previous cycle. Doses in subsequent cycles were reduced by 20% in case of a neutropenic fever episode in the previous cycle, a nadir neutrophil count less than 0.5 x 10^9/l, a nadir platelet count less than 50 x 10^9/l or transient grade 2 and 3 renal toxicity. If more severe renal toxicity occurred, cisplatinum was replaced by carboplatinum at an AUC dose of 6 mg ml/min. All patients underwent response assessment after two cycles. Those with documented progressive disease or stable disease but intolerance to chemotherapy despite dose reductions or those who reported withdrawal of consent were removed from the protocol and given supportive treatment.

Response assessment and statistical analysis:

Complete response (CR) was defined as the disappearance of all clinical and radiological evidence of disease and no new lesions; continuous CR was any CR attained with additional radiation therapy or surgery at any time point of the planned treatment schedule; partial response (PR) as ≥ 50% regression in all measurable lesions; progressive disease as ≥ 25% increase in the sum of the diameters of all measurable sites or the presence of a new lesion. Stable disease (SD) was any response not applicable with CR, PR or PD.

The median progression-free survival from initial treatment to first relapse that marked the initiation of the study regimen was 7.7 months (standard deviation-SD: 1.6, 95% confidence interval: 4.7; 10.7). Survival duration was accepted as the period from the first day of treatment for recurrent and metastatic disease to the time of last contact or death because of disease progression. Survival analysis was performed with the Kaplan-Meier method. Univariate associations with survival duration as a possible end point and selected variables were analyzed by the log-rank test.

Results

Response

All patients received a median four cycles of chemotherapy, ranging between one to six cycles. One patient with a relapsed mass on the vaginal stump received radiotherapy, which resulted in a complete regression of the primary tumor, followed by chemotherapy. This patient was considered to have a continuous complete response (cCR) after the end of the treatment schedule. Two patients (6.7%) could not be evaluated for response to treatment. The overall response rate for all eligible patients was 20% (cCR: 1, CR: 1, PR: 4 patients). Five patients (16.7%) remained with stable disease, while 18 (60%) had progressive disease.

Overall response rate in patients with relapse within the previous radiation field was 9.5%, while that of patients who had recurrent disease outside any irradiated area was 44.4%. There was a substantially higher percentage of patients with progressive disease (66.7%) who relapsed within the previously irradiated area, than those outside the irradiated field (44.4%). More detailed information on this subgroup is given in Table 2.

Table 2. — *Evaluation of response to chemotherapy with respect to site of recurrence.*

	Inside irradiated field		Outside irradiated field	
Response to chemotherapy	n	%	n	%
Complete response	–	–	2	22.2
Partial response	2	9.5	2	22.2
Stationary disease	4	19.0	1	11.1
Progressive disease	14	66.7	4	44.4
Not assessed	1	4.8	–	–

Toxicity

Toxicity assessment was made for 123 cycles administered to 30 patients. Eighteen patients (60%) experienced early withdrawal from the planned schedule, which was due to patient incompliance in seven patients (23.3%), disease progression in ten (33.3%) and early

death with an unidentified cause after the first cycle in one patient (3.3%). As a result, 26.7% of patients were not able to get the planned schedule because of treatment-related problems. Nevertheless, 23 patients (76.7%) received at least three cycles of the study treatment. Anemia was the most frequently encountered toxicity with this combination, necessiating 24 transfusions in nine patients (30%). Detailed data on grade 3 and 4 toxicity according to the WHO criteria are listed in Table 3.

Table 3. — *WHO grade 3 and 4 toxicity.*

	n	%
Hematologic		
Anemia	13	43.3
Leucopenia	1	3.3
Thrombocytopenia	2	6.6
Non-hematologic		
Emesis	9	30.0
Renal	1	3.3
Alopecia	18	60.0

Survival

The median survival duration for all eligible patients was 11 months (SD: 2.4, 95% confidence interval: 6.3; 15.6), ranging between 0.8 to + 50 months. Univariate analysis revealed that progressive response to chemotherapy was the only prognostic factor with a negative impact on survival duration (Figure 1). The median survival for those with progressive disease and those who had an overall response and stable disease to chemotherapy was 7.1 months (SD: 1.2, 95% confidence interval: 4.8; 9.4) and 16.8 months (SD: 5.4, 95% confidence interval: 6.3; 27.2), respectively ($p = 0.003$).

The median survival duration for patients with relapsed disease within the previously irradiated field was 11 months (SD: 2.4, 95% confidence interval: 6.2; 15.6), while that of others who relapsed outside the radiation field was 8.4 months (SD: 4.4, 95% confidence interval: 0; 17) ($p > 0.05$).

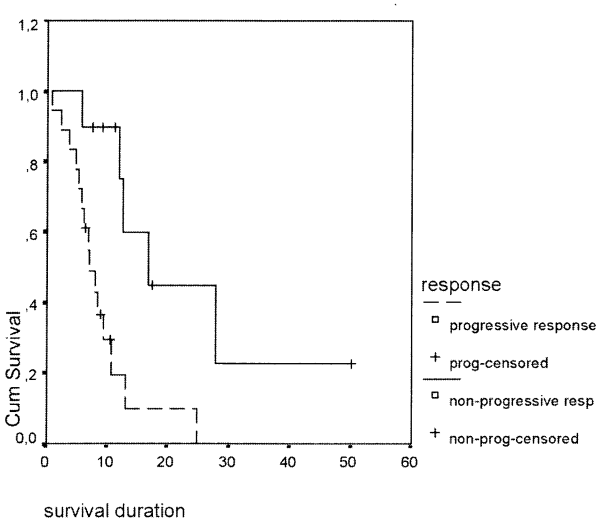

Figure 1. — Significant difference in survival duration with respect to response to chemotherapy.

Discussion

The primary goal of this study was to evaluate the effectiveness of cisplatin and cyclophosphamide as a familiar yet rarely employed doublet. Aside from the study by Jobson *et al.* [10], there has been no direct data reporting the activity of this regimen. In this study the investigators used higher dose levels of both agents, yielding a response rate of 42% at the expense of substantial toxicity and concluded that this combination is encouraging and deserves further investigation [10]. Nevertheless, other trials investigating the activity of similar combinations including cisplatin and cyclophosphamide that have incorporated additional agents such as bleomycin and/or doxorubicin, failed to show an improved outcome for this patient group [11, 12]. Given the activity of both cisplatin and cyclophosphamide in cervical cancer and lack of well established data from randomized studies by the time we initiated our trial, we hoped to get an acceptable response rate and survival duration without significant toxicity.

Based on the results of the study, it appears that the combination of cisplatin and cyclophosphamide at the given doses does not improve the efficacy of single-agent cisplatin. Similar and even higher response rates have been attained by single-agent cisplatin in various studies [13-15]. Nevertheless, the relatively low response rate seems to be related to variances regarding our patient population compared to other non-randomized studies. The short time to progression after initial diagnosis observed in our patient group may also be responsible for the poor response to chemotherapy. Confirming this data, the progression-free interval has been previously determined as a relevant prognostic factor for response to treatment in the recurrent setting [16]. Furthermore, the majority of our patients (70%) had relapsed disease within the previously irradiated area, which is another significant factor that predicts poor response to treatment as confirmed by various studies [16, 17]. The high incidence of progressive response in this subset of patients may be responsible for the poor response rate and is consistent with data from various studies reporting lower response rates and poor survival in this subgroup [5, 17-20]. In concordance with this data, a retrospective analysis of prognostic factors by Cox regression analysis in patients that have been followed in our clinic with metastatic and recurrent cervical carcinoma has revealed that relapsed disease within the previously irradiated field and a progression-free interval of less than eight months are independent prognostic factors with a negative impact on survival (data not shown). All these factors underline a patient group with a relatively poor prognosis and a possibly more aggressive tumor behaviour compared to previous trials that may account for the unexpectedly low response rate.

Univariate analysis has revealed that progressive response to treatment was the only significant variable with an influence on survival. However, considering the wide confidence interval that reflects unreliability most likely due to the small sample size, this data should be evaluated with caution. Nevertheless, this result may also be interpreted as a reflection of the influence of systemic involvement on overall mortality. Other prognostic criteria

such as age, histology, stage at presentation, progression-free interval from initial treatment and menopausal status failed to show a significant association with survival duration of the whole patient group. Despite the lower progressive response in those who relapsed outside the irradiated field, a subgroup analysis did not show a significant survival difference with respect to site of recurrence.

It should also be noted that approximately 25% of the patients could not complete the planned treatment schedule. The relatively high cisplatin dose compared to previous trials, which hardly exceeded 50 mg/m^2 and prior pelvic irradiation are the main factors that contributed to delayed bone marrow recovery and a substantial decrease in performance status. These side-effects may account for the high rate of incompliance and early withdrawal. Apparently, it seems that a lower dose of cisplatin would not only be better tolerated, but also would probably prove to be a more feasible approach so as to achieve a similar survival outcome with less toxicity .

Despite a modest response rate, our patients had a similar survival duration compared to those reported with various regimens, including triple or quadruple combinations and newer generation agents, which are highly toxic. Numerous studies with the mentioned combinations yield response rates in the range of 30-65% and survival ranging between nine and 12 months. Despite the high response rates, few of these trials have resulted in longer survival rates and most, if not all, have reported severe hematologic toxicity reaching 90% in some and gastrointestinal toxicity in about 40% of patients [20-22]. Failure to achieve longer survival, in addition to substantial toxicity confirms the questionable value of multi-drug and expensive regimens employed for purely palliative reasons. Based on the results of this study, the addition of cyclophosphamide to cisplatin at these dose levels has not shown a substantially higher activity than cisplatin alone as a single agent. Until now there are insufficient data that suggest a beneficial role of this regimen or other classical combinations for the treatment of recurrent or metastatic carcinoma of the uterine cervix. Further studies are required to identify a better approach that would improve survival and quality of life in this patient group.

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