Adjuvant Chemotherapy in Locally Advanced Cervical Cancer After Treatment with Concomitant Chemoradiotherapy – Room for Improvement?

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Abstract. *Background: The standard treatment for locally advanced cervical cancer (LACC) is concomitant chemoradiotherapy. In the majority of patients with LACC after properly executed concomitant chemoradiotherapy local control of the disease is achieved, and consequently distant relapse becomes the main cause of death for these patients. In an attempt to improve the outcome of patients with LACC, we designed a regimen of concomitant chemobrachyradiotherapy with cisplatin and ifosfamide followed by consolidation chemotherapy. Patients and Methods: Between 1999 and 2012, 118 patients diagnosed with LACC, The International Federation of Gynecology and Obstetrics (FIGO) stages IB2-IVA, regardless of histology, were treated with concomitant chemobrachyradiotherapy and consolidation chemotherapy at our Institution. Chemotherapy consisted of two cycles of cisplatin and ifosfamide applied concomitantly with two intracavitary low-dose rate brachytherapy applications, and of four cycles of the same drug combination as an adjuvant/consolidation part of the treatment. The primary outcome in this analysis was distant disease-specific survival. Results: A total of 18 patients had documented relapse of cervical cancer, with only three local recurrences observed; 15 patients developed only distant recurrence, and one patient developed both local and distant recurrence. The distant disease- specific survival after a median follow-up of 96 months was 86.4%. Conclusion: Consolidation or adjuvant chemotherapy that follows concomitant chemoradiotherapy has a potential role in further improving control of the disease, especially distant control of the disease.*

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Cervical cancer is a global health problem in women. With almost 500,000 new cases worldwide, and a mortality rate of 60%, the majority in developing regions of the world, it represents a cancer type with still unmet therapeutical needs (1). Lack of prevention programs and, consequently, higher-grade tumor stages at diagnosis in less developed countries, are important reasons for its high incidence and lethality. The standard treatment for locally advanced cervical cancer (LACC) is concomitant chemoradiotherapy. Despite significant clinical benefit, and overall survival gain accomplished with this approach, we are still facing a rather high mortality rate in patients with LACC of The International Federation of Gynecology and Obstetrics (FIGO) stages IB2 to IVA (2-4). For the majority of patients with LACC, after properly executed concomitant chemoradiotherapy, local control of the disease is achieved, and consecutively distant relapse becomes the main cause of death for these patients (2-4).

With the aim of improving outcome of patients with LACC, we designed a regimen of concomitant chemobrachy-radiotherapy with cisplatin and ifosfamide followed by four cycles of consolidation or adjuvant chemotherapy (5). Adjuvant chemotherapy is the absolute gold standard in therapy of many tumor types (6-8). The question is, does it work in cervical cancer? What is the existing evidence for this? Why do we not have a properly designed, powered and executed phase III clinical trials for patients with LACC?

We present the results of our retrospective analysis of consolidation or adjuvant chemotherapy for 118 patients treated at our Institution between 1999 and 2012, and try to answer some of the questions raised above.

Patients and Methods

A total of 118 patients diagnosed with LACC between 1999 and 2012, eligible for our regimen, *i.e.* with FIGO stages IB2-IVA, regardless of histology, were treated with concomitant chemobrachyradiotherapy and consolidation chemotherapy at our Institution-as previously described (9). Pre-treatment diagnostic evaluation consisted of a gynecological examination and a panel of

laboratory and radiological tests: hematology and biochemistry blood test, chest radiography, computed tomographic/magnetic resonance imaging scan of the abdomen and pelvis, and intravenous urography.

The minimum requirements for application of chemotherapy were a total leukocyte count greater than 3×10^9/l, an absolute neutrophil count greater than 1.5×10^9/l, thrombocytes greater than 150×10^9/l, and a creatinine clearance greater than 50 ml/min.

During the pelvic radiotherapy part of the treatment (technique described in our previously published articles) two low-dose rate brachyradiotherapy insertions were performed 3 weeks apart (5, 9). Each brachyradiotherapy application delivered 30 Gy to point A. Chemotherapy was applied concomitantly with brachyradiotherapy: cisplatin, at a dose of 75 mg/m^2 over a 1-h infusion on day 1, in combination with ifosfamide, at a dose of 2,000 mg/m^2 over a 24-hour infusion with adequate premedication, pre- and posthydration, and with mesna uroprotection.

Consolidation chemotherapy was scheduled to begin 4 weeks after the second concomitant chemobrachyradiotherapy cycle. Cisplatin was administered in the same dose on day 1, together with 2,000 mg/m^2 ifosfamide in a 3-hour infusion on days 1-3, for four 3-weekly cycles.

During treatment and before each cycle, patients were evaluated for toxicity by clinical assessments and complete blood counts.

After completion of the whole treatment, the disease status and the treatment-related toxic effects were evaluated by means of history taking, gynecological examination, biopsy of the cervix, computed tomographic scan of the abdomen, a complete blood count and blood biochemistry. Thereafter, patients were evaluated on a 3-montly basis, by history taking, gynecological examinations and blood counts in the first two years of follow-up, every four months in the third year, and every six months thereafter.

Toxicity was assessed at each follow-up using World Health Organization criteria. Data on patients were analyzed using Microsoft Excel (Microsoft, Redmond, WA, United States) and SPSS 21 (IBM, Armonk, NY, USA) The primary outcome of this analysis was distant disease-specific survival.

Results

Between 1999 and 2012, 118 consecutive patients diagnosed with LACC who were eligible for our protocol were treated accordingly. The median follow-up was 99.3 months. Baseline characteristics of the patients are presented in Table I.

All patients received the full course of concomitant chemobrachyradiotherapy. Nine patients did not receive consolidation chemotherapy (five due to persisting hematological toxicity and four because of their age or worsened Eastern Cooperative Oncology Group (ECOG) status). Overall, 80% of patients received four or more cycles of chemotherapy. The median time interval between the consolidation chemotherapy cycles was 27.5 days. The tumor complete response rate at the end of chemobrachyradiotherapy part of the treatment was 100%. All patients were assessed for acute toxicity during treatment. Hematological toxicity was the most prominent, with anemia occurring in 85% of cycles (6.9% of grade 3 or 4) and leucopenia in 81.1% (34.2% of grade 3 or 4). Anemia was corrected with vigorous blood transfusions. Leucopenia and neutropenia were managed with granulocyte colony-stimulating factor application and dose reductions in further cycles. Severe nausea and vomiting (grade 3 or 4) were noted in small number of cycles (4.1% for both toxicities).

A total of 18 patients had documented relapse of cervical cancer, and three patients were diagnosed with new primary tumors. Only three local recurrences occurred. One patient developed both local and distant recurrence with retroperitoneal lymph node involvement as the first site of distant spread. Fifteen patients developed only distant recurrence. The most frequent first site of distant recurrence was in the retroperitoneal lymph nodes and lungs, followed by liver, brain and bone. The median time to distant recurrence was 16.6 months (range=3.0-108.6 months). Figure 1 shows the Kaplan–Meier distant disease-specific survival estimate.

We lost three patients to follow-up and 39 patients had died (18 from cervical cancer and 21 from other causes) by the time of analysis. The Kaplan-Meier curve of disease-specific survival (DFS) and overall survival (OS) for all patients was published previously (9).

Discussion

While early stages of cervical cancer can be successfully treated with surgery, concomitant chemoradiotherapy based on cisplatin is the standard treatment for LACC. Incorporation of concomitant chemotherapy into radiotherapy schedules is in fact the most recent major breakthrough in treatment of LACC at the end of the 1990's when results of five randomized studies comparing concomitant chemoradiotherapy with radiotherapy alone in this setting were published (2-4, 10, 11). Despite an overall survival gain accomplished with concomitant chemoradiotherapy, unfortunately, a significant proportion of patients, 30-40%, are still dying from LACC (2-4, 10, 11).

Whilst local control is becoming reality in therapy of patients with LACC (80-100%), distant control of the disease has become the major issue (12). Perez *et al*. reported, in an era of radiation-therapy only, a 10-year actuarial incidence of distant metastases of 3% in stage IA, 16% in stage IB, 31% in stage IIA, 26% in stage IIB, 39% in stage III, and 75% in stage IVA LACC (13). In patients who develop distant metastases, the most frequently observed sites of metastasis were lung (21%), bone (16%), para-aortic nodes (11%), abdominal cavity (8%), and supraclavicular nodes 7% (14). In contrast, concomitant chemoradiotherapy studies report lower incidence of distant metastases. The incidence of distant relapse ranges between 7% and 11% in lower stages of the disease (IA2-IIA), and between 16% and 22% in higher stages of the disease (IIB-IVA) (3, 10, 11, 15). Consequently, there is obviously an urgent need for a new therapeutic modality that will reduce the incidence of distant metastases of patients with LACC.

Table I. *Baseline characteristics of the patients included in this study.*

Characteristic	No.	%
No.	118	100
Age, median (range), years	52.7 (27-77)	
FIGO stage		
IB2	13	11.0
IIA	16	13.6
IIB	65	55.0
IIIA	0	0
IIIB	21	17.8
IVA	3	2.6
Tumor grade		
1	13	11.0
2	77	65.2
3	18	15.2
Unknown	10	8.6
Tumor histology		
Squamous cell carcinoma	108	91.5
Adenocarcinoma	8	6.7
Adenosquamous carcinoma	2	1.8
Average baseline haemoglobin level (g/l)	120 g/l	
Number of chemotherapy cycles applied		
6	60	50.8
5	27	6.8
4	27	22.9
3	14	11.9
2	9	7.6
0 or 1	0	0

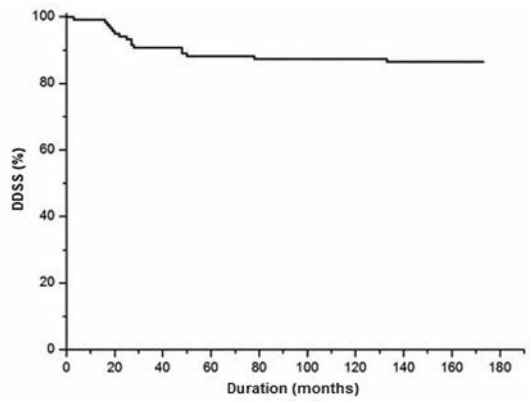

Figure 1. *Kaplan–Meier curve for distant-disease-specific survival (DDSS) after median follow-up period of 96 months for patients with locally advanced cervical cancer treated with concomitant chemobrachyradiotherapy followed by consolidation therapy.*

Adjuvant chemotherapy is a standard -of -care for treatment of many solid tumor types such as of the breast, colon or lung. The response rates achieved by standard chemotherapy regimens, also used in adjuvant settings in treatment of metastatic colonic cancer, are in the range of 20-50%, and for lung cancer they do not exceed 50% (16, 17). Nevertheless, when these regimens are used in an adjuvant setting they improve distant control and overall survival by 20-40% in relative, and 4-10% in absolute terms (18, 19).

Relative chemosensitivity of cervical cancer can be demonstrated in studies of first-line chemotherapy regimens for therapy of metastatic cervical carcinoma, including platinum compounds and ifosfamide, with response rates of 31%-62% (20-22). Moreover, the same chemotherapy regimens when applied in the neoadjuvant setting yield response rates in the range of 80-85% (23, 24). According to these data, it seems justified to hypothesize that such an approach, *i.e.* application of adjuvant or consolidation chemotherapy, might result in better distant control rates in patients with LACC after concomitant chemoradiotherapy.

In our study regarding the role of consolidation, adjuvant chemotherapy was to consolidate local control of the disease achieved by concomitant chemoradiotherapy and to eradicate potential distant micrometastases. The rate of distant metastases in our study after a median follow-up time of 96 months was 13.4% and local failure 2.5%.

Considering that our patient population had rather high tumor stages, from IB2 to IVA, with the majority of patients having IIB or IIIB stage of the disease, this recurrence rate is one of the lowest reported so far, and in our opinion warrants further investigation and proof of concept. Although we are aware of a lack of randomized comparison of concomitant chemoradiotherapy *versus* the same treatment plus consolidation chemotherapy in our work, and inherent drawbacks of a retrospective analysis, our results are in line with those of others reporting that chemotherapy for cervical cancer plays an important role, and that more chemotherapy means greater distant cervical cancer control. For example, Peters *et al*. showed that one to two adjuvant chemotherapy cycles translated to statistically significantly better OS and progression-free survival (PFS) than only concomitantly applied chemotherapy (p=0.03) (10). Similarly, other phase III trials, such as these published by Wong *et al*. (25), and Duenas-Gonzales *et al*. (15), although again not designed to specifically address the question of adjuvant chemotherapy, indirectly point-out that the more chemotherapy we give, the better distant control we provide, and consequently, the better is the overall survival of these patients. In line with previously published results, Tang *et al*. recently published a rather interesting study with patients with LACC having only adenocarcinoma histology and receiving one cycle of neoadjuvant chemotherapy, standard concomitant chemoradiotherapy as part of therapy followed by two consolidation cycles of chemotherapy (26). After a median follow-up of 60 months, they found a statistically significantly longer DFS, OS and local control rate (p<0.05, for all end-points) for patients receiving neoadjuvant and adjuvant chemotherapy. They also noted a difference in the distant

failure rate: 23.6% in the chemoradiotherapy arm *versus* 14.3% in the neoadjuvant/adjuvant plus chemoradiotherapy arm ($p<0.05$). Moreover, the meta-analysis of all randomized trials of concomitant chemoradiotherapy *versus* radiotherapy alone, with all limitations of chemotherapy applied (mostly monotherapy and given exclusively during radiotherapy), have shown a clear and statistically and clinically meaningful impact on distant disease control, 29% reduction in occurrence of distant metastasis, and 12% absolute improvement in overall survival ($p<0.0001$) (12). In contrast to these results, some smaller studies failed to show any positive impact of adjuvant chemotherapy in treatment of LACC (27, 28).

Taking into account that adjuvant chemotherapy is a cornerstone in treatment of so many types of solid cancer, based on the results of our and previously stated studies, we feel it is high time a well-designed randomized controlled study was conducted, properly evaluating the role of adjuvant/consolidation chemotherapy in treatment of LACC. Consolidation or adjuvant chemotherapy that follows concomitant chemoradiotherapy has a potential role to further improve control of the disease, especially distant control of the disease. When designing new regimens for the successful treatment of LACC, we must take into consideration their cost and feasibility, due to the fact that the majority of cases are diagnosed in undeveloped countries. Consequently, we have to design the adjuvant part of therapy based on easily affordable, generic drugs.

Finally, we cannot end this report without stressing once again the lack of investment in cervical cancer research, both clinical and basic (29). This translates into slow development in this field, leading to unsatisfactory treatment results, even in initially non-metastatic disease, a high recurrence rate, and, together with lack of successful further treatment options, an unacceptable mortality rate.

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