Results of Radiotherapy and Concomitant Cisplatin Chemotherapy in Locally Advanced Squamous Cell Carcinoma of Uterine Cervix

SHAHARYAR N SHAMI Z ALAUDDIN A MAHMOOD I MAHMOOD M CHAUDHRY M HUSNAIN Z RASOOL M FAROOQ A J HUSSAIN S ASIF.

Departments of Clinical Oncology (Radiotherapy), Allama Iqbal Medical College and King Edward Medical College, Department of Gynaecology, Allama Iqbal Medical College, Lahore.

Correspondence to: Dr. Shaharyar, Associate Professor of Clinical Oncology (Radiotherapy), King Edward Medical College, Lahore.

From June 1994 to May 1998, 38 patients with histopathologically proven locally advanced stage IIB - IVA squamous cell carcinoma of uterine cervix were treated with radiotherapy and concomitant cisplatin chemotherapy. Radiotherapy was delivered with the combination of high energy external beams and intracavitary high dose rate radiation applications. Eighty one to eighty five Gy was delivered to point A. Cisplatin was given at a dose of 50 mg/m^2 on Day 1 and Day 22 during external beam radiotherapy and subsequently on first intracavitary insertion at day 40 and on last intracavitary insertion around Day 55. Late toxicities were seen in 15.78 % and included rectovaginal fistula, vesicovaginal fistula and rectal ulcers. Overall response was seen in thirty four (89.47%) patients. Complete responses were seen in 65.79% patients and partial response in 23.68% patients. Overall survival of 60 % was achieved. It is concluded that radiotherapy and concomitant cisplatin chemotherapy in these patients of locally advanced squamous cell carcinoma of uterine cervix has provided good survival probability and is associated with manageable acute and late toxicities.

Key words: Chemoradiotherapy, carcinoma uterine cervix, cisplatin

Radiotherapy provides good local control in stage I B and II A carcinoma of uterine cervix, and treatment failures usually present as metastatic disease. However, in patients with locally advanced stage IIB-IVA disease local failures are common with radiotherapy alone. In order to improve the results of radiotherapy various approaches have been tried and include the use of neoadjuvant chemotherapy followed by definitive radiotherapy, concomitant chemotherapy and radiotherapy, adjuvant chemotherapy and use of radiosensitizers. Neoadjuvant chemotherapy has not been shown to improve the results[1]. Concomitant chemotherapy and radiotherapy has been used employing hydroxyurea, 5-flourouracil, mitomycin and cisplatin.

Cisplatin is the most suitable agent for concomitant use with radiotherapy for a variety of reasons. Firstly, cisplatin based chemotherapies have shown tumour shrinkage in 50% of patients with metastatic cervical cancers[2]. Secondly, it has radiosensitizing and synergistic effects with radiation[3]. Thirdly, in cisplatin based combination chemotherapies it has shown improved results[4,5]. Inhibition of sub-lethal radiation damage repair and sensitization of hypoxic cells has been postulated as a mechanism of cisplatin activity[6]. In the light of this data we planned this study of radiotherapy with concomitant cisplatin chemotherapy in treatment of locally advanced stage IIB -IVA carcinoma of cervix. Earlier trials with cisplatin doses of 25 mg/m^2 per week have failed to show any improvement[7]. Therefore, a larger dose and a different schedule was selected for this trial.

This study documents the acute and late toxicities and survival in patients treated with radiotherapy and concomitant cisplatin chemotherapy.

Patients and methods

From June 1994 to May 1998, 38 patients with histopathologically proven squamous cell carcinoma of uterine cervix were treated at Department of Clinical Oncology (Radiotherapy) of Allama Iqbal Medical College and Department of Clinical Oncology (Radiotherapy) of King Edward Medical College, Lahore. Majority of these patients were investigated and biopsied at Gynaecology Department of Allama Iqbal Medical College, Lahore. Clinical staging system of FIGO was used and staging workup included bimanual pelvic and rectal examination, chest X-ray postero/anterior view, abdomino-pelvic ultrasonography, intravenous urography and barium enema. When required, cystoscopic and proctoscopic biopsies were performed to confirm stage IV-A disease. For inclusion in the study, patients were required to have histopathologically confirmed squamous cell carcinoma of uterine cervix, FIGO stage II B, III or IV-A disease, age between 18-65 years, and a normal renal and hepatic function. Adequate bone marrow function with a haemoglobin level of >9gm/dl or tranfused to >9g/dl before definitive treatment was required.

No previous chemotherapy or radiotherapy was allowed. Patients with a history of pelvic inflammatory disease or inflammatory bowel disease or patients with concomitant second malignancy were excluded from the study.

Thirty eight patients fulfilled the eligibility criteria. Patient characteristics are give in Table 1. Thirty patients were treated at Jinnah Hospital/ Allama Iqbal Medical College with 15MV photon beam of a linear accelerator and high dose rate brachytherapy equipment. All patients

were simulated with radio-opaque markers in vagina to outline the distal extent of tumour. Tumour volumes included primary disease and the lymphatic trapezoid. Upper margins of the whole pelvis external beam were placed at L4-5 interspace and lower borders were extended to introitus for vaginal involvement. A 2 cm margin, lateral to the bony-pelvis was included. 40 Gy were delivered to whole pelvis with parallel opposing fields after which a 2cm wide 5HVL block was placed at midline and parametria were radiated to a total dose of 55Gy. Four intracavitary applications of 7.5Gy each were made with 5-7 days interval to achieve a dose of 30Gy to point A. These patients received a total dose of 85Gy at point A. Eight patients were treated at Mayo Hospital / King Edward Medical College using a cobalt beam for whole pelvis external beam radiotherapy. A four field box technique was used and a dose of 45Gy was delivered. This was followed by four intracavitary insertions of 9Gy each delivered by high dose rate brachytherapy equipment. A total dose of 81 Gy was reached at point A. Doses were also calculated for bladder and anterior rectal wall and were kept below threshold.

Cisplatin was given at a dose of 50mg/m^2 on Day 1 and Day 22 during external beam radiotherapy and subsequently on first intracavitary insertion at day 40 and on last intracavitary insertion around Day 55 thus completing the treatment within 8 weeks.

Response to treatment was evaluated at 4 and 8 weeks after completion with clinical and radiological assessment and then subsequently every two months. Response evaluation was done in accordance with WHO criteria[8]. For acute toxicities RTOG / EORTC acute radiation (and chemotherapy) morbidity scoring system was used and for late sequale RTOG / EORTC late radiation morbidity scoring system was used[9]. All toxicities attributable to treatment were recorded.

Table 1 Patient Characteristics (n=38)

Age:	18-65 years
Median age:	48 years
FIGO stage:	
II B	15
III A	7
III B	14
IV A	2
Haemoglobin at presentation	
< 9 g/dl*	16
9-11 g/dl	14
> 11 g/dl	8
Karnofsky's performance status	
Range	70-100
Median	90

*Transfused to > 9 g/dl before treatment

Results

Thirty-six patients received planned cisplatin chemotherapy doses. Two patients received only 3 courses. Planned radiotherapy was completed in all patients. The whole treatment was completed within 8 weeks. All patients were evaluable for toxicity and survival.

Grade 2 nausea and vomiting occurred in 20 out of 38 (52.63%) patients. Grade 3 diarrhea occurred in 6 (15.78%) out of 38 patients. Late toxicities are shown in table 2. Palliative colostomies were constructed for patients with rectovaginal fistula. For patients with vesicovaginal fistula urinary diversion with ileal conduit was made. Rectal symptoms were alleviated with repeated steroid enemas and supportive measures.

Table 2 Grade 4 Late Toxicities (n=38)

Toxicity	No	%age
Rectovaginal fistula	2	5.26
Vesicovaginal fistula	2	5.26
Rectal ulcer	1	2.63
Proctitis	1	2.63
Total	6	15.78

Overall response was seen in thirty four (89.47%) patients. Complete responses were seen in 25(65.79%) patients and partial response in 9(23..68%) patients. Three (7.89%) patients had stable disease and one (2.63 %) patient progressed despite treatment. Relapses were seen in 16(42.11%) patients. Twelve (31.58 %) patients had local pelvic relapse only, 2(5.26%) patients had distant metastases only and 2(5.26%) patients had both local pelvic relapse and distant metastases.

By June 2000, 15 patients had died and 23 patients were alive. Overall survival of 60% is shown in figure 1. Out of 23 alive patients 11 were in stage IIB, 4 were in IIIA and 8 in IIIB.

Discussion

Acute toxicities have been surprisingly limited to grade 2 nausea and vomiting and grade 3 diarrhea only. However, late toxicities have been significant with a grade 4 late toxicity in 15.78% patients. Major toxicities included rectovaginal fistula, vesicovaginal fistula and rectal ulcers. However, no small bowel obstruction or rectal stricture was seen. Others have reported a similar rate of late toxicities (16%) but have also included deep venous thrombosis and pulmonary embolism[10].

Non-randomized trials of chemoradiotherapy incorporating cisplatin have yielded variable response and survival rates. Response rates have varied from 44-81% and overall survival has ranged from 40-60%[11,12]. In our study, a high overall response rate of 89.47% and a complete response rate of 65.79% has been achieved. The responses achieved in our series seem to be higher than the responses seen in non randomized trials.

Many randomized trials have been conducted which have used cisplatin or cisplatin based combination chemotherapies concomitantly with radiation therapy. Five such major trials have been considered as the most representative. Three of these trials on stage IIB - IVA

patients have shown that the survival rates can be improved from 30 to 50%[13-15]. In GOG / SWOG trial on 388 patients with stage IIB -IVA disease patients were randomized to receive either cisplatin plus 5-flourouracil or hydroxyurea with concomitant standard radiotherapy. In cisplatin plus 5-flourouracil and radiotherapy group 63% five years survival was achieved, whereas, in hydroxyurea plus radiotherapy group 47 % five year survival was acheived[13]. Similarly another trial in which cisplatin plus 5-flourouracil plus radiotherapy was tested against extended field radiotherapy 5 year survival rates of 73% was seen in chemoradiotherapy group and 58% in radiotherapy group[14]. The third trial had IIB - IVA patients randomized to cisplatin group, cisplatin plus 5-flourouracil plus hydroxyurea group and a hydroxyurea group concomitant with standard radiotherapy in all three arms. Five year survival rates were 66%, 64%, and 39% respectively[15]. Fourth trial was on stage IB patients and fifth trial was on stage IB and IIA high risk patients.[16,17]. However, 30-50% reduction in relative risk of relapse and death was seen in all five trials. These results led National Cancer Institute of America to issue a clinical alert to physicians strongly recommending the concomitant use of cisplatin and radiation therapy in the treatment of invasive cervical cancer. Our figures of 60 % overall survival represent that we have possibly been successful in translating the benefits of chemoradiotherapy in this group of patient population. We have also previously reported a successful outcome on a small series of patients treated with concomitant cisplatin chemotherapy and radiotherapy in comparison to radiotherapy alone[18].

In sharp contrast to the results of the above cited five major studies a recent report on 259 patients of stage IIA - IIB disease has shown that the weekly cisplatin plus radiotherapy and radiotherapy alone have similar results[19]. Infact this is the only randomized trial which has directly addressed the outcome of adding cisplatin to radiotherapy without any other treatment. Three year survival rates in cisplatin plus radiotherapy group and radiotherapy alone group were 69% and 66% respectively whereas five year survival rates were 59% and 56% respectively. It seems reasonable to infer from these conflicting reports that the exact benefit of chemoradiotherapy needs to be further explored in large scale trials. It is also possible that a metaanalysis of all existing data may further clarify the extent of benefit. However, till such time, this approach can be considered as a new standard of care.

Conclusion

It is concluded that radiotherapy and concomitant cisplatin chemotherapy in this patient population of locally advanced squamous cell carcinoma of uterine cervix has achieved a good survival probability and is associated with manageable acute and late toxicities.

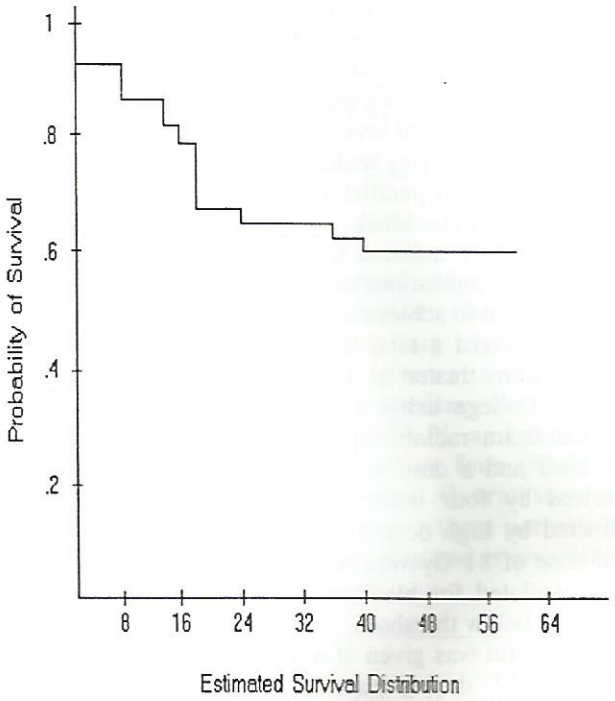

Figure 1: Overall Survival Analysis by Kaplan-Meier Method

Fig. 1. Overall survival analysis by Kaplan-Meier Method

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