Cisplatin MTX Chemotherapy Before Radiotherapy Improves Survival in Cancer Cervix

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Summary

The US National Cancer Institute strongly recommend use of Chemotherapy in cases of cancer cervix as the first line of treatment followed by Surgery or Radiotherapy. This reduces the risk of death by 30 to 50% as compared to conventional therapy. Between September 1994 and December 1998, 78 patients with FIGO stage IIA to IVB squamous cell carcinoma of cancer cervix were entered into the study. Patients age ranged from 32 to 78 years (median 46) Median performance status was 2(ECOG) All patients received inj Cisplatin 50mg/m2 infusion on Day 1 with MTX 50 mg intravenous push every 3 weeks. Patients were then subjected to complete Radiotherapy treatment. Out of the 78 patients entered in the study only 69 patients were evaluable to response. Forty seven patients (68.1%) responded to the chemotherapy. Patients with good performance status showed good response to chemotherapy. The median survival among the responders is significantly higher at 24 months as compared to only 8 months among the non responders. Twenty seven patients are alive and disease free at an interval of 10 to 48 months (median 29) from beginning of chemotherapy. The chemotherapy toxicity was mild and there were no chemotherapy deaths. Moreover the overall cost of treatment is only Rs. 400-Rs 500. The present study confirms that Cisplatin MTX regimen is an active combination in patients of advanced cervical cancer with simple method of administration, good response, minimal toxicity and acceptable cost.

Introduction

Prognosis of patients with advanced metastatic cervical cancer is generally poor. A worldwide alert to doctors to change the way in which they treat cervical cancer has been issued by the U S National Cancer Institute. They strongly recommend use of Chemotherapy in cases of cancer cervix as the first line of treatment followed by Surgery or Radiotherapy. This reduces the risk of death by 30 to 50% as compared to conventional therapy.

Cisplatin is the most effective single agent against cervical cancer. Many workers (Kumar & Bhargava 1991 Buxton et al 1989; Singhal et al 1993) have shown that combination protocols using bleomycin, ifosfomide and cisplatin have shown improved response rate compared to cisplatin alone. However the toxicity is moderate and survival is not significantly improved The cost of treatment ranges from Rs. 3000 to 3500 per cycle which is not affordable to many as cancer cervix is the disease of the poor. Methothrexate a highly active antifolate agent has shown significant activity in squamous cell carcinoma of Head andNeck. Therefore a protocol using Cisplatin and MTX was used and the results are discussed here.

Material and Methods

Between September 1994 and December 1998 78 patients with FIGO stage IIA to IVB squamous cell carcinoma of cancer cervix were entered into the study.

Patients age ranged from 32 to 78 years (median 46) Median performance status was 2(ECOG). All patients were examined jointly by a team of medical oncologist and a gynecologist. A detailed history was taken. Clinical evaluation, performance status, haemogram, urine, renal and liver function tests, creatinine clearance and X ray chests of all patients was done. Ultrasound was done to determine the tumor size and to assess renal status and response to chemotherapy.

As shown in Table I. All patients received inj Cisplatin 50mg/m2 infusion on Day 1 with MTX 50 mg intravenous push every 3 weeks. Ondansetron, Metoclopramide and folic acid from Day 2 were given to control nausea/vomiting and mucositis. Toxicity and response to chemotherapy was assessed according to the WHO criterias. (Miller et al 1981).

Table I
Chemotherapy regimen

Inj. Cisplatinum	50mg/m2 IV infusion Day 1
Inj MTX	50 mg IV push Day 1
To be repeated every 21 days	

During treatment, blood counts were done once a week. Clinical examination to evaluate response and a S.creatinine level were done prior to every cycle. Repeat radiological studies (ultrasound, chest X ray) were done after 3rd and 6th cycle of chemotherapy according to WHO criteria. Patients were then subjected to complete radiotherapy treatment.

Survival was defined as the time from beginning of chemotherapy to date of death or date of censoring (December 1998).

Results

Out of the 78 patients entered in the study only 69 patients were evaluated. Four patients were lost to followup after 3-4 cycles of chemotherapy or incomplete radiotherapy. One patient developed severe mucositis, 2 developed grade II renal failure and 1 developed infective hepatitis so further cycles were withheld. A 76 years old patient suffered an ishcaemic heart attack and died.

The mean age of the patients was 46 years. One patient had II A disease while 29 patients had II B disease, 5 had III A disease, 37 had III B disease and 6 had IV A disease. (Table II) Seventy Four percent of the cases had a bulky disease. Forty four patients had a performance status between 0-2 while 34 had a performance status of 3-4. Out of the 34 patients with poor performance status 2 had IIB disease, 4 had IIIA disese, 22 had IIIB disease and 6 had IVA disease. Twenty six patients were more than 55 years of age.

Table II
Patients characteristics

Age (years)	
Median	46
Range	32-78
Performance status	
0-2	36
3-4	42
Median	2
Original FIGO stage	
IIA	1
IIB	29
IIIA	5
IIIB	37
IV A	6
IV B	0

Forty seven of 69 patients did well with complete response in 22(31.9%) cases and partial response in 25(39.1%) cases. Ten patients showed minimal response while 12 had either no response or progressed while on chemotherapy. The median overall survival for all eligible patients is 18months (range 2 to 50 months). The median survival for chemotherapy responders and non-responders is 24 months and 8 months respectively.

As shown in Table III out of the 22 complete responders, 16 patients are alive, 14 are disease free at a median of 30 months (8 to 48 months) and 2 had recurrence of disease after 21 months and 27 months. Six patients have died of disease at 8,18,19,25,29 and 36 months after beginning of chemotherapy. Out of the 25 partial responders, 11 are alive and 8 are disease free

Table III Response to chemotherapy and survival

Response	Total	Alive	Disease Free	Recurrent disease	Died	Median Survival (months)
CR	22	16	14	2	6	28
PR	25	11	8	3	14	21
CR+PR	47	27	22	9	20	-
Minimal	10	0	0	0	10	10
Progressive	12	0	0	0	12	6

with median survival of 19 months (range 6 to 25 months). Three patients are undergoing chemotherapy for recurrent disease and 14 have died after a mean duration of 12 months.

All patients who had minimal response or progressive disease also showed poor response to radiotherapy and succumbed to the disease with median survival of 10 and 6 months respectively.

A total of 453 cycles of chemotherapy were administered and 12 patients showed grade II or more toxicity (Table IV). Twenty two patients showed fall in hemoglobin and anemia of which 18 had grade I, 3 had grade II and only one had grade III anemia requiring blood transfusion. Almost all patients experienced nausea but this was managed by antiemetic regimen. Only 1 patient required adminission. While 11 patients suffered from constipation lasting for 4 to 5 days after chemotherapy and responded well on simple laxatives. Only 1 patient developed grade III ototoxicity and 2 had grade II ototoxicity. Ten patients had grade II alopecia. Most of them recovered their hair after 3 months of stopping chemotherapy. One patient developed grade III mucositis and further chemotherapy was stopped. Seven patients had grade II mucositis and folic acid supplements were given. There were no chemotherapy related deaths in present series.

Table IV
Toxic effects of chemotherapy

Toxic effects	WHO			
	I	II	III	IV
Anemia	18	3	1	0
Leukopenia	8	2	0	0
Nausea/vomiting	31	16	1	0
Constipation	6	4	1	0
Ototoxicity	4	2	1	0
Renal insufficiency	2	2	0	0
Alopecia	0	10	0	0
Mucositis	4	7	0	0

The total cost of therapy varied from Rs. 400 to Rs. 500 per cycle.

Discussion

The present study evaluated the use of Cisplatin + MTX combination chemotherapy followed by Radiotherapy in patients of advanced cancer cervix. Forty seven patients (68.1%) responded to chemotherapy which is comparable to the results of Kumar & Bhargava 1998, Buxton et al 1989 and Singhal et al 1993 52.2%, 69% & 66.6% respectively. The present study shows a slightly better response as all the patients received neoadjuvant chemotherapy while the other studies had some patients who had undergone previous surgery or radiotherapy. Following radiotherapy there is a compromised blood flow in the affected area reducing the local concentration of chemotherapy leading to poor response. (Kumar and Bhargava 1991).

The response rates followig Cisplatin MTX were also significantly higher to those obtained with Cisplatin alone. Complete and partial response was 68.1% in the present study as compared to only 17.8% in the Gynecologic Oncology Group (GOG) by Omara et al (1997) and 30% by Kumar and Bhargava (1998) when cisplatin alone was used.

The response to chemotherapy depended highly on the performance status of the patient at the initiation of the treatment. Patients with good performance status showed good response to chemotherapy. Seventy five percent of the responders had good 0-2 performance status.

The median survival among the responders is significantly higher at 24 months as compared to only 8 months among nonresponders. Twenty seven patients are alive and disease free at an interval of 10 to 48 months (median 29) from beginning of chemotherapy. This shows that chemotherapy with radiotherapy can achieve few long term survivals even in advanced cervical cancer,(Kumar and Bhargava 1998).

The chemotherapy toxicity was mild and there were no chemotherapy deaths. The toxicity was significantly lower to other combination protocols using Bleomycin, Ifosfamide, VP 16 etc (Kumar and Bhargava 1998, Buxton et al 1989) As compared to the popular BIP regimen this protocol can be given on Day 1 with no need for admission. Moreover the overall cost of treatment is only Rs. 400-Rs.500 as compared to approximately Rs. 3500-Rs.4000 in the BIP regimen.

The present study confirms that Cisplatin MTX regimen is an active combination in patients of advanced cervical cancer with simple method of administration, good response, minimal toxicity and acceptable cost.

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