CISPLATIN IN TREATMENT OF ADVANCED AND RECURRENT SQUAMOUS CELL CARCINOMA OF CERVIX.

A.C. KATAKI ● B.C. GOSWAMI

SUMMARY

Twenty patients with advanced and recurrent squamous cell carcinoma of the cervix no longer amenable to control with surgery and/or radiotherapy were treated with cisplatin 100mg/m2 every 3 weeks. Three patients achieved complete response (4, 6 and 8 months) and seven patients achieved partial response. The median duration of response was six months and median survival 11 months in the responders. 35% and 15% patients achieved objective response with pelvic and extra-pelvic disease respectively. Adverse effect included primarily gastroi-ntestinal toxicity.

INTRODUCTION

Results of chemotherapy in advanced and recurrent cervical cancer have been disappointing (Wasserman et al, 1977). A total of 38 cytotoxic agents have been tested in squamous cell Ca cervix. Coleman et al (1986) and Meanwell et al (1986) reported response rate of 40% and 33% respectively in patients with advanced or recurrent carcinoma cervix with iphosphamide.

Cis-platinum (Cis-diammine dichloroplatinum) was first introduced into clinical trials in 1972 (Higby et al). In a phase II clinical trial by gynaccologic oncology group (GOG) using single agent cisplatin in advanced squamous cell carcinoma cervix, a 50% objective response was achieved (Thigpen et al, 1980). An attempt is made in the present study to see the response of single agent

Dr. B. Barooah Cancer Institute, Guwahati.
Accepted for Publication on May 96

Cis-platin in advanced and recurrent squamous cell carcinoma of cervix.

MATERIALS AND METHOD

The present study was carried out at Dr. B. Borooah Cancer Institute, Guwahati from July, 1993 to April, 1995. Twenty patients with advanced and recurrent squamous cell carcinoma of cervix previously treated with radical radiation therapy, radical surgery and surgery and radiation therapy with no prior chemotherapy were included for this study.

Only those patients with measurable disease and GOG performance grade of 0 to 2 were eligible. Pretreatment evaluation incuded physical examination, laboratory evidence of adequate renal function (BUB < 20mg/100 ml, creatinine < 1.5mg/100 ml, creatinine clearance > 70ml/min) WBC count > 4000/mm3, platelet count > 100,000/mm3 and Haemoglobin > 10.0gm/dl.

Cisplatin 100mg/m2 of body surface area was given at 3 weekly interval depending upon the response and continued until toxicity precluded further treatment or disease progressed. Pretreatment hydration and post-treatment diuresis was given to avoid nephrotoxicity. Ondansetron 8 mg. I.V. and Dexamethasone 4 mg I.V. was given prior to chemotherapy and repeated after 4 hours. Ondansetron 8 mg tab. twice daily was given subsequently for three days to avoid nausea and vomiting. The following response criteria was followed during the study : complete response (CR) -disappearance of all clinical evidence of disease for atleast one month; partial response (PR) - a> 50% reduction in the product of perpendicular diameter of each measurable lesion for atleast one month; Progressive disease (PD) - a > 50% increase in the product of perpendicular diameters of any measurable lesion or the apperanace of any new lesion less than one month after entry into the study; Stable disease (SD) - a < 50% regression or progression of lesion.

Response duration was defined as time from documentation of objective response (CR + PR) to date of reappearance of, or documentation or increasing parameters of or to date of last contact. Survival was defined as the observed length of life from entry into study to death or the living patients, date of last contact.

RESULTS AND OBSERVATIONS

The characteristics of 20 patients who completed more than 3 courses of chemotherapy and were evaluable are presented in Table I.

Ten out of twenty patients achieved an objective response (50%) to therapy with three (15%) of these achieving a complete response (4, 6 and 8 months). The median duration of response was six months with no difference between complete and partial responses. Median survival was 11 months for responders, whereas non responders demonstrated a significant shorter median survival of less than six months. Response by site

Table I
CHARACTERISTICS OF THE STUDY POPULATION

Age in years (range) 44	(29-64)
Time in months from diagnosis to recurrence (range)	14.5 (4-56)
Performance status	
0 (Fully active)	7/20
1 (Restricted in physically strenuous activities)	8/20
2 (Restricted in all activities but ambulatory)	5/20
Prior therapy	
Radiotherapy	10/20
Surgery and ratiotherapy	6/20
Surgery only	4/20

Table II
RESPONSE BY SITE OF DISEASE

Response	Pelvic Disease	Extrapelvic Disease
Complete response	2	1
Partial response	5	2
Stable disease	3	5
Progressive disease	1	1

of the disease are shown in Table II & III.

In 2 patients (10%) the disease progressed during treatment. One patient had hepatic metastases and the other central pelvic recurrence. Thirty five percent of patients with local pelvic disease achieved objective response,whereas only 15% of patients with extra pelvic disease achieved objective response of variable duration.

Adverse effects consisted of primarily of nausea, vomiting, myelosupression and nephrotoxicity. Gastrointestinal toxicity in the form of nausea and vomiting was the most frequent adverse effect other toxicity noted mild fever (2 cases),

Table III
PATIENTS WITH EXTRAPELVIC METASTASES

atient	Site of Involvement	Method of Measurment	Response
.	Lung	Chest X-ray	Stable 6 months
.	Lung	Chest X-ray	PR 7 months
.	Liver	Abdo. USG	PD
.	Spine	X-ray spine	PR 5 months
.	Lung, Pelvis	Chest X-ray palpation	Stable 3 months
.	Para-aortic node	USG	Stable 5 months
.	Pelvis central	Palpation	Stable 6 months
-9.	Inguinal and or supraclavicular L. node	Palpation	1 CR 8 months 1 Stable 4 months

Table IV
COMMONLY OBSERVED ADVERSE EFFECTS

dverse effect		No. of patients
eucopenia	3000 - 4000/ul	2/20
	2000 - 3000/ul	1/20
	1000 - 2000/ul	1/20
hrombocytopenia	100000 150000/ul	3/20
	90000 - 100000/ul	1/20
ausea and Vomiting		
	Mild	10/20
	Moderate	2/20
	Severe	1/20
ephrotoxicity		
ild (BUN 21 - 40 mg/dl; creatinine .3 - 2.0mg/dl)		5/20
oderate (BUN 41 - 60mg/dl; creatinine .1 - 4.0 mg/dl)		1/20

mild clinical hearing loss (1), carpopedal spasm (1 case), peripheral neuritis (1 case). Different toxicities encountered are shown in Table IV.

DISCUSSION

Results of treatment of patients with advanced or recurrent squamous cell carcinoma of cervix with chemotherapy have not been characterized by overwhelming success. Responses were observed in approximately 20% or fewer and were transient in duration with no survival benefit for patients. More recently higher frequency of response has been reported, but the duration of response has still been relatively short with little survival bebefit. Cohen et al (1978) in a series of 11 patients treated with Cisplatin at a dose of 120 mg/m2 at 3 weekly interval, achieved partial responses in 5 cases. Young et al (1979) used Cisplatin 50mg/m2 body surface area because of lack of evidence of a dose response relationship with platinum. Bonomi et al (1985) reported response rates varying from 20 to 40%, complete responses from 8 to 12% and a median response duration of 3 to 5 months using Cisplatin alone.

The median duration of response of six months in the present study exceeds that reported for other regimens, as does the median survival of 11 months (Baker et al 1977). Thigpen et al (1981) in a series of 22 patients using single agent Cisplatin achieved objective response in 11 (50%) patients with a median response duration of 6 months and median survival of 9 months in responders.

Adverse effects in the present study population were tolerable with no drug related death noted. Myelosupression was mild in nature. Perhaps most significant from the patient point of view was gastrointestinal toxicity. Nausea and vomiting were virtually universal but less severe due to ondansetron and dexamethasone. Kataki et al (1995) reported excellent control of nausea and vomiting (90% response rate) in 40 patients with gynaecological cancer treated with cisplatin based chemotherapy along with ondansetron and dexamethasone. Nephrotoxicity was relatively mild due to adequate pretreatment hydration and post-treatment diuresis.

CONCLUSION

Cisplatinum is clearly an active drug in the therapy of squamous cell carcinoma of the cervix. Further studies are needed to answer the question of a possible dose response relationship as well as to identify other active agents which may be combined with cisplatinum to seek more frequent and longer lasting responses.

REFERENCES

1. *Baker L.H., Opipari M. J. Am Soc Clin. Oncol 18 : 272, 1977.*
2. *Bonomi P., Blessing J.A., Stehman F.B., DiSaia P.J., Walton L., Major F.J., J. Clin. N. Am 30 : 1511, 1985.*

3. *Cohen C.L., Castro-Marin A. Deppe G., Bruckner H.W., Holland J.F., Proc. Am. Soc. Clin. Oncol. 19 : 401, 1978.*
4. *Coleman R.E., Harper P.G., Gallagher C. Cancer Chemother Pharmacol, 18 : 280-1986.*
5. *Higby D.J., Wallace H.J. Jr., Holland J.F., Cancer Chemother Rep, 57 : 459-, 1973.*
6. *Kataki A.C., Goswami B.C., Sharma C.N, 39th AICOG Abstract, 109, Dec. 1995.*
7. *Meanwell C.A., Mould J.J., Blackledge G. Cancer Treat Rep., 70 : 777-, 1986.*
8. *Thigpen T., Shingleton H., Homsley H. Lagasse L. and Blessing J. Cancer, 48 : 899-1981.*
9. *Wasserman T.H., Carter S.K., Cancer Treat Rew., 5 : 25, 1977.*
10. *Young R.C., Von Hoff D.D., Gormley P. Cancer Treat Rep., 63 : 1539-, 1979.*