Asian Journal of Pharmaceutical and Clinical Research
Vol. 4, Issue 1, 2011 ISSN - 0974-2441

Research Article

TOXICITIES AND TOLERANCES OF THE CANCER CERVIX PATIENTS

R. BASKARAN, B. ANTOINETTE MARY NITHIYA

Department of Chemistry and Biotechnology, St. Joseph's College of Engineering, Chennai, India.
E-mail: rbaskaran2000@yahoo.com

ABSTRACT

Purpose: Cancer cervix is the second commonest malignancy among women globally to affect the female population in developing countries. The highest incidence rates are reported from Asia, South America and Africa. In India, cancer cervix is the commonest malignancy among women with an incidence of over 1, 00,000 new cases annually. Every patient must know the tolerance limits of the toxicities when they undergone for radiation treatment.
Patients and methods: Cancer cervix constitutes 20 – 50% of all cancers detected in our women. Most of the women belong to lower socioeconomic stratum. The present work is assessing the acute toxicities and tolerances of the cancer cervix patients obtained by Hyperfractionated radiotherapy with Cisplatin based concurrent chemotherapy weekly, followed by Brachytherapy.
Results: The bone marrow suppression was more in the study due to the combined effect of increased RT dose to the pelvic haemotopoietic tissues and chemotherapy.
Conclusion: Patients had grade-l toxicity 16% and grade –2 toxicity only 4% Manifestation of this toxicity was in the form of increased frequency of micturition with associated dysuria which was effectively managed with anti-biotics and plenty of oral fluids. The impact of this regime on long term survival as well as the long term morbidity associated with this protocol is to be analysed in the future.

Key words: 1, 5 benzothiazepines, Green synthesis, CNS activity.

INTRODUCTION

The major prerequisite for the development of cancer cervix are female sexual behavior and sexual intercourse. Women who start their sexual life at an early age particularly before 18 years are at 1.4 to 1.9 times increased risk of developing cancer cervix. Cancer cervix patients usually give a history of multiple sexual partners. The risk is doubled for women with 6 sexual partners. Risk factors related to parity include first childbirth at an early age and multiparity. The presence of which is associated with a higher incidence of cancer cervix in their spouses are sexual promiscuity: >3 extra marital partners, history of sexually transmitted disease, history of cancer penis or history of cancer cervix in first wife.
Among various agents, the HPV (Human Papilloma Virus) virus is considered to be the most likely candidate for etiological responsibility. Women who are HIV (Human immunodeficiency virus) positive have a 10 fold risk of cervical cancer in comparison with matched controls. Prevalence of cancer cervix in HIV positive patients below the age of 50 years is 19%. There is much data suggesting an association between cancer cervix and HSV (Herpes simplex virus) but no conclusive proof is available.

PREVIOUS STUDY

Clinicians have been investigating the use of concurrent chemoradiation for many years. The Gynecological Oncology Group has been investigating the role of concurrent chemoradiation in cancer cervix since the early 70's. The early studies concentrated on hydroxyurea a drug used as radiosensitiser. The effectiveness of Cisplatin in producing tumor regression in patients with local recurrence or distant metastasis after primary treatment paved the way for its use in combination with radiation at an earlier stage of treatment. From 1979 patients with advanced cancer cervix started receiving treatment with concurrent Cisplatin based chemoradiation. The overall 5 year survival of the study conducted by Blake et al[1] was 49% for all stages.

A complete remission of 89% was observed for stage III disease. This study suggested that cisplatin based chemotherapy combined with radio therapy could be safely used to treat cancer cervix patients at high risk relax. Various prospective trials for patients with locally advanced cancer were under taken. Potish et al[2] and Twiggs et al[3] administered cisplatin weekly in an effort to increase the response. Fields et al[4] and Runowicz et al[5] conducted phase II trials of concurrent chemoradiation using Cisplatin (Dose 20mg/m^2 day 1 –5 at 21day intervals). The data revealed better disease free survival and overall survival for Cisplatin based regimen. Souhami et al[6] conducted a phase II Prospective trial of 50 patients with locally advanced cancer cervix patients stage IIA- IVA treated with concurrent chemoradiation 30mg /m^2 weekly one day of every week. The total dose to point A was 76Gy. A complete response rate 88%was seen. The actuarial survival rate at 4 years was 65% with acceptable toxicity. The studies like GOG –85[7],GOG –120[8], GOG – 123[9] RTOG –90- 01[10], SWOG –87 - 97[11] showed a consistence advantage in complete response , DFS with reduction in mortality by 30 – 50% over conventional radiotherapy alone.

Hyperfractionated external radiotherapy with brachytherapy in bulky carcinoma cervix was studied in various trials by RTOG. RTOG –85-05[12] trial shows that 1.2 Gy twice daily in ten fractions per week external radiotherapy administered to the whole pelvis with 4 -5 hrs. interval between fractions up to a dose of 48 Gy followed by 1or 2 intracavity applications to deliver a total minimum dose of 85 Gy at point A and 65Gy to parametrium was equally effective as conventional RT was well tolerated and additional 10% parametrial dose was delivered. Since chemotherapy showed increased benefits and hyper fractionated RT delivered more doses to the parametrium respecting the normal tissue toxicity attempts at combining chemotherapy with hyper fractionated RT were made.

Calkins et.al[13] assessed the toxicities of multiple daily fractionated whole pelvis radiation plus concurrent chemotherapy for locally advanced carcinoma of the cervix. Cisplatin 50 mg/m^2 was administered on days 1 and 17 of external radiation, 5 – FU was given by the continuous IV infusion (1gm / m^2) for 4 consecutive days on 2, 3, 4, 5 and 18, 19, 20 and 21.The maximum tolerated dose of whole pelvis radiation that could be delivered in a hyper fractionated setting with concomitant chemotherapy was 57.6Gy in 48 fractions followed by brachytherapy RTOG –92-10[14], this study was designed to administer twice daily radiation doses of 1.2Gy to the pelvis and para- aortic at 4-6hr intervals five days per week.
The total external radiation doses where 24 – 48 Gy to the whole pelvis 12 – 36Gy parametrical boost and 48 Gy to the para-aortic with an additional boost to a total dose of 54 – 58 Gy to the known metastatic para –aortic site.1 or 2 ICA where performed to deliver dose of 85Gy to point A. Cisplatin (75 mg / m^2, day 1 and 22) and 5 FU (1000mg / m^2 / 24hr x 4 days 1 and 22) were given for 2 or 3 cycles. The overall survival estimates were 59% at 1year and 47% at 2years.The study concluded unacceptably high rate (31%) of great four non hematological toxicity. The survival estimates appear no better than standard fractionation RT without chemotherapy. The National Cancer Institute issued a clinical announcement in 1999 stating that cisplatin based concurrent chemoradiation was the new standard of care in a locally advanced cancer cervix.

MATERIALS AND METHODS

ELIGIBILITY CRITERIA

Twenty four patients with locally advanced cancer cervix who satisfied the following eligibility criteria were included in this study.

- Age: 30 - 60 years ; Disease stage: II B – III B
- Performance status: Karnofsky performance score ~ 80
- Histology: squamous cell carcinoma only
- Haematological parameters
  - TC: 4000 and above / cubic mm
  - PLT: 1 lakh and above / cubic mm
  - RBC: 3 million and above / cubic mm

  Haemoglobin > 10 gm%
- HIV negative
- No history of treatment for the same complaints.

THERAPEUTIC PROTOCOL

HYPERFRACTIONATED EBRT- CONCURRENT CHEMOTHERAPY: Hyperfractionated radiotherapy, 57.6Gy of EBRT 120cGy per fraction, twice daily at 6 hours interval for 5 days a week with Cisplatin based concurrent chemotherapy weekly, followed by Brachytherapy

EBRT Equipment**:** Co – 60 Phoenix for Teletherapy
ICA Equipment : HDR Remote after loader Ir- 192
Source : HDR brachytherapy.

EBRT PROTOCOL Dose details

Total dose delivered 57.6 Gy
Dose /# 1.2 Gy / #, 2# a day 6 hours interval by AP portals, both portals treated twice daily
No of fractions 48
Total duration 4 weeks and 4 days
Treatment days /week 5
Patients were assessed for ICA at the end of 48 fractions of external beam radiation.

Procedure of chemotherapy administration

Patient is pre- hydrated with one liter of Ringer lactate solution, 24 hours prior to commencement of chemotherapy during every cycle. On the day of chemotherapy, before administering the drug the patient is hydrated with 500 ml of ringer Lactate solution. This was followed by injection of 4 mg of Ondansetron, 50 mg of Inj. Ranitidine and 100 ml of Inj.

Mannitol 30 minutes prior to onset of Cisplatin administration. This was followed by infusion of 40 mg/m^2 of Cisplatin dissolved in 1 litre of normal saline infused in 2 hours. This was followed by post chemo hydration with 1 litre of Normal saline. Finally 20 mg of Inj. Frusemide was given i.v.

The entire chemo procedure was completed in 4 hours. External beam radiation was delivered within 1 hour of chemotherapy then second fraction 6 hours later. Overall treatment time per patient is 52 days. The patients were to be reviewed every one month for the first six months followed by every 2 months for the next 2 years followed by once every 3 months thereafter.

RESULTS AND DISCUSSION

TOXICITIES

Graded as per RTOG criteria: These included immediate and early reactions.
A. LOCAL: Skin RTOG, Mucosa RTOG, Bladder – RTOG, Rectum – RTOG and Small bowel- RTOG acute morbidity grading criteria are shown in Table 1.

B. SYSTEMIC (Table 2): 1. Hematological 2. Renal
HAEMATOLOGICAL: The only toxicity observed was 87% grade-l leucopenia (TC between 3,000 -4, OOO). The fall in WBC counts was transient and the patients recovered without any treatment.

RENAL: None of the patients showed any renal impairment during the study.

It was observed that the bone marrow suppression was more in the study due to the combined effect of increased RT dose to the pelvic haemotopoietic tissues and chemotherapy. There were no treatment drop outs or treatment related deaths during this study.

ANALYSIS OF IMMEDIATE TOXICITIES IN THE STUDY

All patients in the study were evaluated for skin, vaginal mucosa, upper GIT, bladder, rectal, renal and hematological toxicities in accordance with RTOG criteria. The following data was obtained:
SKIN: There was no grade-3 or grade-4 reactions only 33% of patients had grade-2 reactions.

MUCOSA - We observed only 4% grade -2 mucositis in spite of hyperfractionated schedule.

UPPER GIT - The patients had a greater incidence of grade 2 toxicity (100%) The manifestations of toxicity were predominantly nausea and vomiting which was attributed to the emetic effect of CDDP which added on to that of RT. However all patients were successfully treated with the anti-emetic drug Ondansetron injected as 4mg i.v. b.d. None of the patients developed grade 3 or 4 toxicity.

RECTUM - The patients developed rectal toxicity 8% of patients had grade 3 toxicity. The grade 2(42%) complications observed were mainly in the form of diarrhea and proctitis and these complaints were managed with antibiotics and anti-diarrheal drug Loperamide (tab1 b.d) along with oral hydration.Grade-3 toxicities subsided with suspension of RT for 2 days.

BLADDER - Patients had grade-l toxicity 16% and grade –2 toxicity only 4% manifestation of this toxicity was in the form of increased frequency of micturition with associated dysuria which was effectively managed with anti-biotics and plenty of oral fluids.
The comparison of toxicity patterns of other studies on concurrent cisplatin based chemo-radiation are shown in Table 3 and comparison of toxicity patterns of studies on hyperfractionated – radiation are shown in table 4. Comparison of toxicity patterns of studies con ducted in our instituition are shown in Table 5.

CONCLUSION

Stage of disease, volume of disease, general condition of the patient, performance status are well recognized prognostic factors which influence therapeutic outcome in cancer of the cervix. The sub-group of patients with added benefits over the concurrent chemoradiation studies with acceptable toxicities are i. Stage IIIB disease ii. Younger patient's iii Lower hemoglobin status. The only toxicity observed was 87% grade-l leucopenia. The fall in WBC counts was transient and the patients recovered without any treatment. It was observed that the bone marrow suppression was more in the study due to the combined effect of increased RT dose to the pelvic haemotopoietic tissues and chemotherapy. The patients are on regular follow up for accrual of long term results. The impact of this regime on long term survival as well as the long term morbidity associated with this protocol is to be analysed in the future.

REFERENCES

1. Blake et al - Combined radiotherapy and chemotherapy for advanced carcinoma of the cervix. Clinical radiology 37(5):465-469 Sep 1986.
2. Potish et al - Effect of Cisplatin on tolerance to radiation therapy in advanced cervical cancer. American journal of clinical radiology. Vol 9:387-391, 1986.
3. Twiggs et al - Concurrent weekly Cisplatin and radiotherapy in advanced cervical Cancer. Gynecol oncology 24: 143-148, 1986. 61:416-422,
4. Fields et al - Mature results of a phase- II study on concomitant Cisplatin & pelvic radiotherapy in locally advanced cervical cancer. Gynec oncology 1996.
5. Runowicz et al - Concurrent Cisplatin and radiotherapy in locally advanced cancer cervix. Gynec oncology -34:395-401, 1989.

Table –1: LOCAL - Skin – RTOG, Mucosa RTOG, Bladder – RTOG , Rectum – RTOG and Small bowel- RTOG acute morbidity grading criteria

Grade	Change (Skin – RTOG)
0	No change over base line
I	Follicules, faint or dull erythema, dry desquamation, epilation, decreased sweating.
II	Tender or bright erythema, patchy moist desquamation, moderate edema.
III	Confluent, moist desquamation other than skin folds, pitting edema.
IV	Ulceration, hemorrhage, necrosis.
	(Mucosa – RTOG)
0	No change
I	Erythema
II	Patchy mucositis.
III	Confluent mucositis.
IV	Ulceration.
	(Bladder – RTOG)
0	No change
I	Frequency of micturition nocturia twice that of pre-treatment frequency. Dysuria needing medication
II	Frequency of micturition nocturia less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anaesthetic
III	Frequency with urgency and nocturia hourly or more frequent. Dysuria, urgency, bladder spasm requiring regular narcotic. Gross haematuria with *I* without clot passage
IV	Haematuria requiring transfusion. Acute bladder obstruction not secondary to clot passage. Ulceration or necrosis.
	(Rectum – RTOG)
0	No change
I	Increased frequency or change in bowel habits, rectal discomfort not requiring medication.
II	Diarrhoea requiring para-sympatholytic drug. Mucous discharge, rectal I abdominal pain requiring medication.
III	Diarrhohea requiring parenteral support, mucous or bloody discharge requiring sanitary pads
IV	Acute / sub- acute obstruction, fistula or perforation, GIT bleeding requiring transfusion. Abdominal pain, tenesmus requiring tube decomoression or bowel diversion.
	(Small bowel- RTOG)
0	No change
I	Anorexia with 5% weight loss from base line. Nausea, abdominal pain not requiring medication
II	Anorexia with 15% weight loss from base line. Nausea and vomiting requiring medication.
III	Anorexia with> 15% weight loss from base line requiring NG tube or parenteral support. Severe abdominal pain despite medication. Haematemesis, melena or abdominal distension.
IV	Ileus, sub-acute obstruction, perforation. GIT bleeding requiring transfusion. Abdominal pain requiring tube decompression or bowel diversion.

(P values-not significant)

Table –2: Systemic Toxicity

Systemic effects	RTOG grade of toxicity	No. of patients (%)	P values
Haematological (leucopenia)		21(87 %)	0.711
Renal		nil	-
LOCAL TOXICITY			
Skin	Gr-0	4 (17 %)	0.382
	Gr-l	12 (50 %)	
	Gr-2	8 (33%)	
Vaginal mucosa	Gr-l	23 (96 %)	0.227
	Gr-2	1(4 %)	
Small bowel	Gr-l	-	
	Gr-2	24 (100 %)	
Rectum	Gr-1	12 (50 %)	0.79
	Gr-2	10 (42 %)	
	Gr -3	2(8 %)	
Bladder	Gr-1	16 (66 %)	
	Gr-2	1(4 %)	0.08

(P value-not significant)

Table –3: Comparison of Toxicity Patterns of other Studies on concurrent cisplatin based chemo-radiation

Study	Treatment modality	Organ involved	Toxicity (maximum grades as %)
RTOG-90-01[10]	RT+CDDP	Rectum	GR-4 (8%)
GOG - 123[9]	RT+ CDDP	Hematological	GR-3 (18%) GR-4 (5%)
GOG - 120[8]	RT + CDDP	Hematological	GR-3 (21 %)

Table –4: Comparison of toxicity patterns of studies on hyperfractionated –radiation

Study	RT dose	Organs involved	Toxicity (Max grade as %)
RTOG 88–05[12] (long term follow study done)	1.2Gy b.i.d	Skin Bladder Small bowel	Grade 4 -5% Grade 3 -1% Grade 3 -10%
Accelerated hyperfractionated RT[17]	1.25Gy b.i.d	Vaginal mucosa Small bowel Large bowel bladder	Grade 4- 2% Grade 3- 1% Grade 4- 2% Grade 3- 4%

6. Souhami et al - Weekly Cisplatin and external beam radiation and HDR brachytherapy in locally advanced cancer cervix. Int J Radiat Oncol Biol Phys.
7. Whitney et al-GOG 85 report. Journal of clinical oncology.Vol-17:13391345, 1999.
8. Peter.G. Rose et al - GOG 120 report. NEJM 340(15)1144-1153, April 1999.
9. Henry .M. Keys et a1 - GOG 123 report. NEJM 340(15) 1154-1161, April 1999.
10. Mitchell.Morris et a1 RTOG- 90-01 report. NEJM 340(15)1137-1143, April 1999.
11. Peters et a1 SWOG-87-97 report- Gynec oncology 72: 443-450, 1999.
12. Ritsuko komaki M.D , Thomas F.Pajak, Victor A Marcial Twice daily fractionation of external irradiation with brachytherapy in Bulky carcinoma of cervix RTOG 88-05 Cancer 1994 : 73 : 2619-25.
13. .Alison R Calkins .M.D et.al hyperfractionated Radiation Therapy plus chemotherapy in locally advanced cervical cancer Gynecologic oncology 5:3:349-355 1999.
14. Perry. W. Gregsby .J.D.LU: David Mutch ; Robert Y Kim patricia J Eifel. Twice daily fractionation of external irradiation with brachytherapy and chemotherapy in carcinoma of cervix with positive para – aortic lymph nodes Gynecology cancer working group- Int Jou.Rad Oncology, Biology and physics-51(3) 58-59 , 2001.

Table –5: Comparison of Toxicity Patterns of Studies conducted in our Instituition

Study	Treatment Modality	Organ Involved	Toxicity (max. grade as %)
Hyperfractionated RT	Hyperfractionated EBRT +Brachy	Skin Bladder Small Bowel	Grade-2 ; 10% Grade-2 ; 10% Grade-2 ; 10%
Concurrent Chemoradiation	Conventional RT +Cisplatin D1-5&D21-25	Skin Vaginal mucosa Small Bowel Rectum Bladder	Grade –2 ;50% Grade-1 ;100% Grade-2 ;100% Grade-2 ;50% Grade-1 ;70%
Hyperfractionated RT with chemo	Hyperfractionated EBRT +Brachy +cisplatin D1&17;5FU D-2,3,4,5& D-22,23,24,25	Skin Vaginal mucosa Small Bowel Rectum Bladder	Grade –3 ;11% Grade-2 ;26% Grade-4 ;10% Grade-4 ;4% Grade-2 ;18%
Concurrent chemo-RT with weekly Cisplatin (previous study)	Conventional RT +Cisplatin weekly onD1,6,11,16,21	Skin Vaginal mucosa Small Bowel Rectum Bladder	Grade –2 ;50% Grade-1 ;100% Grade-2 ;100% Grade-2 ;50% Grade-1 ;70%
Hyperfractionated EBRT with weekly cisplatin(present study)	Hyperfractionated EBRT +Brachy+Cisplatin weekly onD1,6,11,16,21	Skin Vaginal mucosa Small Bowel Rectum Bladder	Grade –2 ;33% Grade-2 ;4% Grade-2 ;100% Grade-3 ;2% Grade-2 ;4%