

A PHASE II STUDY OF GEMCITABINE CONCURRENT WITH RADIATION IN LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK: A TRIAL OF THE CANCER RESEARCH GROUP PAKISTAN

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ABSTRACT

Objective: To evaluate the efficacy and toxicity of weekly gemcitabine as a radiosensitizer concurrent with radical radiotherapy in locally advanced carcinoma of head and neck.

Patients and Methods: From August 2001 to January 2002, thirty-nine patients with stage III or IV B inoperable carcinoma of head and neck were enrolled. Patients with histopathologically confirmed squamous cell carcinoma with at least one bidimensionally measurable lesion, no prior chemotherapy or radiotherapy, and a KPS of 60 or above were included. Patients with nasopharyngeal, glottic or sub-glottic cancer were excluded. Gemcitabine 150mg/m² or a total dose not exceeding 200 mg was given on day 1, 8, 15, 22, 29, and 36 during radiation treatment. Radiation was delivered with conventional fractionation to a total dose of 66-70Gy. Miller's criteria was used for response evaluation. RTOG/EORTC acute radiation (and chemotherapy) morbidity scoring system and WHO grading of acute and sub acute toxicity criteria were used for documentation of toxicity.

Results: All 39 patients were evaluable for toxicity but only 35 patients were evaluable for response. An overall response rate of 94.3% (95% CI; 80.8-99.3) was seen with a partial response rate of 71.4% and complete response rate of 22.9% (95% CI; 10.4-40.1). Grade 3 mucositis was seen in 28 patients (71.8%). Grade 4 mucositis was seen in 2 patients (5.1%). Pharyngeal toxicity was the second-most common toxicity. Grade 2 toxicity was seen in 12 patients (30.8%) and grade 3 in 6 patients (15.4%). Despite vigorous symptomatic and supportive care acute toxicities led to treatment interruption in 40% of patients.

Conclusion: A high overall response rate and a high rate of acute toxicity are seen at a weekly gemcitabine dose of 150mg/m² concurrent with radiation. This shows that gemcitabine is a potent radiosensitizer with a marked tumor and normal tissue radio sensitization.

KEY WORDS: Gemcitabine, Radiotherapy, Locally advanced squamous cell carcinoma, Head and Neck Cancer.

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INTRODUCTION

Combined chemotherapy and radiotherapy has become the standard treatment of locally advanced unresectable squamous cell carcinoma of head and neck.¹ Five different randomized trials in unresectable patients have given positive results and have shown improved survival and improved loco-regional control.²⁻⁶ A recent meta analysis has also shown absolute survival advantage for patients with locally advanced squamous cell

carcinoma treated with concurrent chemoradiotherapy.⁷ However a significant increase in mucosal and hematological toxicity is noted in these patients.

A number of older trials have used radiotherapy concurrent with the single radiosensitizing cytotoxic agents like 5 FU, methotrexate, bleomycin and cisplatin.⁸⁻¹¹ Most of these drugs produce enhanced cell killing with radiosensitization because they interfere with cell repair after sub lethal damage, potentially lethal damage or with tumor cell synchronization.^{12,13} In recent trials paclitaxel has been studied concurrent with radiation, as prolonged infusion, weekly infusion or in combination with cisplatin.^{14,15} Paclitaxel induces tumour cell mitotic arrest, a cell cycle blockage at G2 phase-to-mitosis (G2/M) transition and enhances tissue oxygenation contributing to enhanced cell killing by radiation.¹⁶⁻¹⁹ Most of these drugs have been used in cytotoxic doses.

Gemcitabine a pyrimidine analogue is one such chemotherapeutic agent which has shown radio sensitization at non-cytotoxic concentration of 10nmol/l. It has been shown that pre-radiation exposure of HT-29 human colon carcinoma cells to non cytotoxic concentrations of gemcitabine for 24 hours achieves a sensitizer enhancement ratio of 1.8.²⁰ Pancreatic and breast cancer cell lines have also shown significant radiosensitization.^{21,22} Additional studies have shown that with shorter gemcitabine infusion of two hours significant radiosensitization is still evident at 24 hours and cells continue to be sensitized at 48-72 hours.²³

Based on these pre-clinical studies it has been postulated that radio-sensitization with gemcitabine is due to depletion of de-oxyadenosinetriphosphate (dATP) through inhibition of ribonucleotide reductase by the diphosphate metabolite, dFdCDP, and cell cycle redistribution into S phase. When these two conditions are present DNA damage caused by radiation cannot be repaired and this leads to increased cell death.²⁴

Phase 1 clinical studies in squamous cell carcinoma of head and neck have also been

done. They used doses ranging from 50-300mg/m² during radiotherapy and achieved high response rates but with a high overall toxicity. These studies have emphasized the need for further evaluation of radiosensitization by low dose gemcitabine.^{25,26} This phase II multicentric study has been conducted to find out the feasibility and toxicity of concurrent administration of 150mg/m² of gemcitabine and radical radiotherapy in patients with locally advanced squamous cell carcinoma of head and neck.

PATIENTS AND METHODS

The study was carried out in six different oncology centers, collaborating under the Cancer Research Group of Pakistan. All investigators participated in protocol writing and development of case report Forms. Pre-treatment evaluation included complete history and thorough physical examination. Laboratory investigations included complete blood count, alkaline phosphatase, AST, ALT, bilirubin, total protein and albumin level. Complete examination of urine was done. Soft tissues X-rays and CT scan from base of skull to thoracic inlet were obtained. Orthopantogram was optional. Indirect laryngoscopy was performed in all patients. Oesophagoscopy for lesions involving esophagus was carried out. Barium swallow was obtained in all laryngopharyngeal tumors. Chest X-ray posteroanterior view, ECG and ultrasonography of abdomen and pelvis were carried out. For TNM categorization and staging, UICC system for classification of malignant tumors was used.²⁷

Eligibility criteria included histopathologically confirmed squamous cell carcinoma of the head and neck, with locally advanced disease (stage III-IVB) who were otherwise candidates for radical radiotherapy. Presence of at least one bidimensionally measurable lesion was required. No previous chemotherapy or radiotherapy was allowed. Adequate marrow function with white blood cell count of 4000/cu mm, platelet count of 100,000/cu mm and hemoglobin 9gms/dl were required. Patients below 70 years of age were included provided

they had KPS of 60 or above. A voluntary, written and witnessed informed consent from patient or guardian was obtained in all cases.

Patients with previous or current other malignancies with the exception of adequately treated carcinoma in situ of cervix and basal or squamous cell carcinoma of skin were excluded from the study. Patients with inadequate renal function with creatinine ≥ 1.25 times upper limit of normal or inadequate liver function with bilirubin ≥ 1.5 times upper limit of normal or ALT or AST ≥ 3 times normal were also excluded. Patients with bone or cartilage invasion as a sole criterion of a T4 lesion were not allowed. Nasopharyngeal, glottic, or sub-glottic cancers were also excluded from the study.

Body surface area of the patient was calculated according to height and weight at the beginning of each dose of gemcitabine. Gemcitabine 150mg/m² or a total dose not

exceeding 200 mg was given on days 1, 8, 15, 22, 29, and 36 during radiation treatment.

Gemcitabine was reconstituted with normal saline to make a solution containing 10mg/ml and was administered intravenously in an adequate amount of saline over two hours. Radiation was delivered two hours after the completion of gemcitabine infusion. Conventional fractionation was used to a total dose of 66-70Gy. Lateral opposed portals with cobalt 60 beam or 6 MV photons were used for primary tumor and upper neck and an anterior low neck field was used to cover cervical lymph nodes. Spinal cord dose was limited below 40Gy. Brain stem and optic nerves were restricted at 54Gy. Gastric tube feeding was planned for patients with severe mucositis.

Methods of Evaluation: All patients completing first week of treatment were evaluable for toxicity. RTOG/EORTC acute radiation (and chemotherapy) morbidity scoring system and WHO grading of acute and sub acute toxicity criteria was used.^{28,29} Acute toxicity was evaluated on a weekly basis.

All patients who received a minimum of 40Gy and four doses of weekly gemcitabine were evaluable for response. The responses were evaluated at the discontinuation or completion of treatment protocol and subsequently one month after the last evaluation. Assessment was done with physical examination and CT scans and responses were evaluated according to Miller's criteria.²⁸

Patient Characteristics: Thirty-nine patients of squamous cell carcinoma were treated in a period of six months between August 2001 and January 2002. Patient demographics and disease characteristics at baseline are given in Table-I.

Treatment Administration: A total of 210 radiosensitizing doses of gemcitabine were delivered. Of the 39 enrolled patients, 1 patient declined gemcitabine after the first dose, 3 patients received only three doses each and were also not evaluable for response, 2 patients received four doses each and remaining 33 patients received all six doses. Fourteen patients (35.89%) had treatment interruptions

Table-I: Patient Characteristics.

Age	Median	52 years		
	Range	36-68 years		
Sex:	Male	28		
	Females	11		
KPS	70	10 (25.64%)		
	80	17 (43.59%)		
	90	10 (25.64%)		
	100	02 (05.13%)		
Tumor Site:	Oral cavity	15 (38.46%)		
	Oropharynx	06 (15.38%)		
	Hypopharynx	11 (28.21%)		
	PNS	04 (10.26%)		
	*Others	03 (07.69%)		
*Single site of region could not be assigned:				
Stage	N0	N1	N2	N3
T2	—	—	—	02
T3	01	01	02	03
T4	06	07	13	04
Maximum Size:	Median	07 cm		
	Range	2-12 cm		

for less than two weeks and two patients (5.13%) for more than two weeks. In these patients, both gemcitabine and radiation were withheld.

RESULTS

Response: Thirty-five patients were evaluable for response. Complete response was seen in eight patients (22.86%)(95%CI; 10.4-40.1) and partial response in 25 patients (71.43%) with an overall response rate of 94.29% (95% CI; 80.8-99.3). All partial responses were evident in the first evaluation at four weeks of treatment, and by completion of 6 weeks, 5 out of 8 complete responses were evident. Twenty-five patients achieved a 50% or greater reduction in tumor size, of which 20 patients had greater than 75% reduction in volume of disease. Only one patient (2.86%) each had stable disease or disease progression.

Twenty patients who were followed for a longer period included two complete responders and 18 partial responders. At a median follow up of 22 months (range,8-28 months), two patients are alive without disease, and 12 patients are alive with disease and are receiving palliative care or second line treatment. Out of these 20 patients six have died so far, two at home of massive bleeding, and four in hospital with evidence of progressive disease. *Toxicity:* Acute toxicity is given in Table-II and III. All thirty-nine patients were evaluable for toxicity. Grade 3 mucositis was observed in 28 patients (71.79%) and grade 4 in two patients (5.13%). Mucositis started two weeks after starting the treatment and continued for 7-21 days after last radiation was given. Tube feeding was performed in 11 patients. Feeding stoma was required in four patients

Grade 3 pharyngeal toxicity was seen in 6 (15.4%) patients only. One patient developed pharyngo-cutaneous fistula after third dose of gemcitabine and 21 fractions of radiation and died of massive bleeding. This patient had carotid encasement on pre-treatment CT scan. Skin toxicity was grade 2 in majority of patients except one patient who developed grade three skin toxicity. Late toxicity was

Table-II: Acute toxicity; RTOG / EORTC criteria (n=39)

	G1 No.(%)	G2 No.(%)	G3 No.(%)	G4 No.(%)
Mucosal	-	06(15.38)	28(71.79)	02(5.13)
Pharyngeal	04(10.26)	12(30.77)	06(15.38)	01(2.56)
Skin	04(10.26)	04(10.26)	01(2.56)	-

evaluable in 22 patients only. Grade 4 pharyngeal toxicity was seen in two patients who developed pharyngeal obstruction in the fifth month of follow up. Eighteen patients had grade 2 sub-cutaneous tissue damage.

DISCUSSION

This phase II study of gemcitabine as a radiosensitizer at a dose of 150mg/m² in locally advanced squamous cell carcinoma of head and neck demonstrates our ability to do multicentric cancer research in Pakistan where oncology as a discipline is not yet fully established. Head and neck patients in this part of the world have predisposing and aggravating factors of beetle nut chewing and the use of spit tobacco. These patients have altered oro-pharyngeal mucosa with gingival recession, periodontal bone and soft tissue damage, loss of periodontal attachment, tooth abrasion, leucoplakia and sub-mucus fibrosis. Treatments developed in other patient populations need to be re-confirmed before their general use can be safely recommended in these patients.

A 94.29% overall response rate was achieved in this study for patients with advanced squamous cell carcinoma of head and neck. This response rate is comparable to those achieved with concomitant 5-fluorouracil, cisplatin and radiotherapy,³⁰ and also to those in two other studies in head and neck cancer using

Table-III: Acute toxicity; WHO grading (n=39)

	G1 No.(%)	G2 No.(%)	G3 No.(%)	G4 No.(%)
Neutropenia	04(10.26)	-	-	-
Leucopenia	06(15.38)	04(10.26)	-	-
Nausea/ Vomiting	16(41.03)	04(10.26)	01(2.56)	-
Infection	16(41.03)	10(25.6)	01(2.56)	-
Fever	14(35.90)	10(25.6)	02(5.13)	-

gemcitabine as radiosensitizer. In a phase II study, utilizing 200mg/m² of gemcitabine during radiotherapy, a 70% ORR with a 15% CR was seen.²⁵ In another phase I study, endoscopic and tumor bed biopsies of patients receiving 150mg/m² of gemcitabine with radical radiotherapy revealed a pathologic response in 8 out of 10 patients.²⁶ The ORR seen in our present study is the highest ever reported, however our 23% CR rate is quite low, and is probably related to frequent interruptions leading to split-course type radiotherapy that may allow tumor cell repopulation during the breaks.

Response in majority of our patients was achieved rapidly and was evident by the fourth or fifth week of treatment. This rapidity of cell kill achieved by radiation and gemcitabine indicates efficacy of gemcitabine as radiosensitizer manifesting as enhanced tumor cell kill for a given dose of radiation. This is in confirmation of high sensitizer enhancement ratio of 1.7 to 3 seen in pre-clinical studies.²³ It is important to note that higher sensitizer enhancement of 1.5 or greater is considered optimal.³¹ With radiotherapy alone, complete and partial responses have not been reported by fourth or fifth week of treatment.

Grade 3 mucositis and dysphagia were the most common acute toxicities of this regimen. These seem to be greater than the toxicities seen with radiation alone in some studies but are comparable to the use of concurrent 5-fluorouracil, cisplatin and radiation and various schedules of paclitaxel and radiation.³²⁻³⁵ Studies using hyper-fractionated radiotherapy concurrent with 5-fluorouracil and cisplatin show a similar rate of confluent G3 mucositis but the reported G4 mucositis is less.³⁶

Confluent mucositis and dysphagia leads to treatment interruption in a significant number of patients and more effective remedies than supportive and symptomatic care alone are required to avoid the treatment interruption. Radioprotector amifostane was one such expectation but early results indicated that at conventional dosing, it did not prevent the mucositis though it effectively reduced the

acute and chronic xerostomia, while still preserving the anti-tumor effect.³⁷ However, in recent reports it has been shown to be effective in reducing mucositis and dysphagia resulting from chemoradiotherapy in head and neck cancer patients.³⁸

If such compounds become available, to reduce the toxicity, the radiation therapy with radiosensitizers will become the most effective way to treat head and neck cancers. The limiting factor in the curability of SCCHN is that the tumoricidal doses cannot be delivered without exceeding the normal tissue tolerance. The therapeutic window is relatively narrow. However, with effective radiosensitizers like gemcitabine the equivalent tumor cell kill can be achieved by using lower total dose of radiation and therefore possibly without exceeding the normal tissue tolerance. This assumption would be only valid if it can be demonstrated that normal tissues are either not radiosensitized at all or are less radiosensitized than tumor cells. No such drug has been proven to have selective tumor cell radiosensitization. Paclitaxel in some studies have shown a preferential radiosensitization in tumor cells but in majority of other studies, the skin damage and mucositis is marked enough to deny this finding. Greater cell kill for a given radiation dose indicates a possibility that the lower total dose might be equally effective to increase the tumor control probability for a given level of normal tissue complications. Further trials are clearly required to evaluate this approach with low dose gemcitabine and lower total dose of radiotherapy. Early achievement of partial and complete responses seen in fourth and fifth week in this trial also favor this approach.

It is of interest to note that different tissues in the human body tolerate different radiosensitizing doses of gemcitabine. Unacceptable toxicity occurred in lung cancer patients treated with 1000mg/m² per week during radiation therapy.³⁹ Pancreatic cancer patients on the other hand tolerated 600mg/m² of gemcitabine with a 50.4Gy dose of radiotherapy.⁴⁰ This can be explained by

considering the possibility that duodenal mucosa might have a different tolerance to radiosensitizing effects. Similarly the different sites of oral cavity and oropharyngeal mucosa might show different radiosensitizing potential and further site-specific studies might utilize this deferential to improve the therapeutic ratio.

CONCLUSION

A high overall response rate and a high rate of acute toxicity was observed in this protocol at a weekly gemcitabine dose of 150mg/m² given concurrently with radiation. This study suggests that gemcitabine is a potent radiosensitizer with a marked tumor and normal tissue radiosensitization.

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