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Comparative study of Gemcitabine versus Cisplatin concurrent with radiotherapy for locally advanced head and neck cancer

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Abstract: PURPOSE: In our study we compared low-dose gemcitabine-based chemoradiotherapy with cisplatin-based chemoradiotherapy as regards response rate, survival and toxicity profile in locally advanced head and neck cancer. Methodology: sixty patients with locally advanced head and neck cancer were included in this prospective comparative randomized study, in the period from January 2011 to September 2013. Results: The patients were treated in two randomized groups; each of them included 30 patients. In gemcitabine arm (group A), 42.3% of the patients had stage III, and 57.7% of them had stage IVa while 48.15% of the patients of cisplatin arm (group B) had stage III and 51.85% had stage IVa. The median duration of response in group A was 21 months, while in group B it was 23 months. The degree of response had a statistically significant effect on survival in group B patients. It was evident in patients who achieved partial response (PR) that showed lower survival than those with (CR). Conclusion: Gemcitabine has comparable radiosensitizing effect with acceptable toxicity profile and can be used as a radiosensitizer in head and neck cancers especially when cisplatin cannot be used. We recommend further studies to establish its rule.

Keywords: Head and Neck, Radiotherapy, Chemotherapy, Gemcitabine, Cisplatin

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide with a global annual incidence of 500,000. HNSCC is a heterogeneous group of cancers, with a variable, but usually poor prognosis (1). Despite advances in treatment, the mortality rate of HNSCC has not changed markedly over the last few decades. Besides the poor outcome, head and neck cancer has a great impact on the patient's quality of life, due to its anatomic location. Treatment of head and neck cancers usually affect patient quality of life, as it may results in disfigurement, it can affect speech, breathing and swallowing (2). Systematically designed randomized studies established a role for chemotherapy as part of the standard combined modality management of squamous cell head and neck cancer in several settings. These included the therapy of unresectable disease, for organ preservation, and for patients with poor risk pathologic features after surgery. An update of the results of the Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) evaluated 63 randomized trials published from 1965 through 1993, all of which compared locoregional treatment with or without chemotherapy was reported and confirmed the superior efficacy of concurrent therapy (3).Concurrent chemoradiotherapy (CRT) has been shown to be superior to radiotherapy (RT) alone in several clinical therapeutic settings for head and neck cancer. CRT is

superior to RT alone in unresectable disease, as well as for resectable advanced disease, and it may serve as a substitute for initial surgery, with planned salvage surgery as a backup. Also In the postoperative setting, clinical trials suggest that CRT is superior to RT alone. (4). Many of these trials showed that the combined regimen was superior to radiation therapy alone in locoregional control or organ preservation. Two trials also showed improvement in overall survival (5). Gemcitabine was reported to be one of the most-potent radiosensitizers for treating locally advanced HNSCC, which was confirmed in many trials, (6) and (7). In previous phase II trial done by one of the authors of the current study Fifty-two patients with locally advanced HNSCC (stage III, 50%; stage IVa, 50%) were enrolled. All received a course of radiotherapy (70 Gy over 7weeks) concurrent with weekly infusions of gemcitabine at 50 mg/m2. Severe mucositis (grade 3-4) was observed in 76% of patients.

Severe hematological toxicity was uncommon. Xerostomia was the most-common late toxicity in 34 patients (65.4%). The rate of complete and partial response rate was 67.3% and 21.1%, respectively, with an overall response rate of 88.45%. Two years progression-free survival and disease-free survival were 46% and 38.46%, respectively (8).

2. Patients and Methods

Sixty patients, with locally advanced head and neck cancer, were included in this prospective comparative randomized study, during the period from January 2011 to September 2013, at Clinical Oncology and Nuclear Medicine Department, Sohag Faculty of Medicine. In our study we included patients with histopathologically proven squamous cell carcinoma of the head and neck, with stage III and IV (nonmetastatic) disease, age ≥18 and ≤70 years, adequate hematological, renal, and hepatic functions, ECOG performance status 0 and 1, no prior therapy, including chemotherapy, radiotherapy and or therapeutic surgery. No history of other malignancies.

2.1. Pretreatment Evaluation

History and physical examination, head and neck examination, dental evaluation with management of dental problem and oral hygiene prior to the start of radiation. Any tooth with periodontal disease or dental caries was extracted before radiation therapy. The radiation therapy started 5- 7 days after extraction to allow adequate healing of the tooth socket. All included patients had CT scan or MRI study of the primary site and draining lymph nodes. Chest X-ray and abdominal ultrasonography were done. Rigid and fibro-optic pan-endoscopy was done to assess the nose, paranasal sinuses, nasopharynx, oropharynx, larynx, hypopharynx and esophagus. We reported the following: Gross criteria of the primary lesion including the site, size, shape, extension, consistency and vocal fold mobility (in laryngeal and hypo pharyngeal malignancies) for accurate evaluation of T stage, careful inspection to detect possible other primaries or precancerous lesions. Biopsy was taking from the advancing edge of the tumor.

Randomization: Sixty patients, were eligible and enrolled in the study, they were randomly assigned to the treatment arms.

Ethical consideration: The study was reviewed and accepted by the University Ethics Committee before enrollment. All study details were discussed with the included patients and they were informed that they can withdraw from the study at any point. All included patients signed an informed study-specific consent prior to enrollment in the study.

2.2. Chemotherapy

Group A (tested regimen): Gemcitabine was administered intravenously over 30 minutes once weekly at the first working day of the week, two hours before radiation, at 50 mg/m2 for 7 consecutive weeks (the period of radiotherapy).

Group B (standard regimen): Cisplatin was administered intravenously over two hours, at 100 mg/m2 with pre and post chemotherapy hydration, on day 1, 22 and 43 of radiotherapy (three cycles during the period of radiotherapy).

Radiotherapy for group A and B: Prior to treatment, all radiological and endoscopic studies were interpreted to plan the target volumes. Parallel opposed lateral fields, with patients immobilized in a supine position were used. The borders of the fields were determined according to the location of the primary tumor and known extension by CT findings and endoscopy. Radiotherapy was delivered once daily, five days a week as a single 2 Gy fraction. The total dose administered was 70 Gy, intended to be delivered over seven weeks. Gross target volume (GTV) including the primary tumor and gross palpable lymph node were treated with 70 Gy. The maximum dose to the spinal cord was restricted to 46 Gy.

3. Results

Sixty patients with locally advanced head and neck squamous cell carcinoma were included in this study. It was conducted at the Clinical Oncology and Nuclear Medicine Department, Sohag Faculty of Medicine during the period from January 2011 to September 2013. The patients were randomized in two groups; each of them included 30 patients. Seven patients were excluded from the study, four patients from group A (tested regimen) were excluded from the study, one of them died from cerebral infarction developed at week 4 of treatment, and the other three patients discontinued treatment at week 4 and 5 of treatment and missed follow-up. In group B (standard regimen), Three patients were excluded because of discontinuation of treatment at week 5 and 6 and missed follow-up. Patient's characteristics were balanced between both groups. Table (1).

Table (1). *Patients' characteristics*

Characteristics	Group A	Group B	P value
	No (%)	No (%)	
Sex			
Female	8 (30.77%)	5 (18.52%)	0.30
Male	18 (69.23%)	22 (81.48%)	
Age			
<50	8 (30.77%)	7 (25.93)	0.70
≥50	18 (69.23%)	20 (74.07)	
Mean (SD)	53.73 (±11.35)	56.29 (±12.14)	0.26
Median (range)	54 (25-70)	57 (22-69)	
Performance status			
0	1 (3.85%)	0 (0.0%)	0.07
1	12 (46.15%)	14 (51.95%)	
2	13 (50.00%)	13 (48.15%)	
Smoking			
No	12 (46.15%)	6 (22.22%)	0.07
Yes	14 ((53.85%)	21 (77.78%)	
Baseline HGB			
Mean (SD)	12.39 (±1.89)	12.35 (±1.13)	0.58
Median (range)	12 (9.9-15.8)	12 (10.5 – 16)	

3.1. Tumor Stage

Table (2). *Tumor's characteristics*

characteristics	Group A	Group B	P value
	No (%)	No (%)	
Site of primary tumor			
NPX	2 (7.69)	6 (22.22)	
Cheek	0 (0.0)	1 (3.7)	
Hypopharynx	4 (15.38)	3 (11.11)	0.15
Larynx	13 (50.00)	16 (59.26)	
Paranasal sinus	2 (7.7)	1 (3.7)	
Tongue	5 (19.23)	0 (0.0)	
T stage			
T1	2 (7.69)	0 (0.0)	
T2	6 (23.08)	8 (29.63)	0.51
T3	10 (38.46)	11 (40.74)	
T4	8 (30.77)	8 (29.63)	
N stage			
N0	5 (19.23)	11 (40.74)	
N1	5 (19.23)	9 (33.33)	0.03
N2	16 (61.54)	6 (22.22)	
N3	0 (0.0)	1 (3.71)	
Pathological grade			
I	2 (7.69)	8 (29.63)	
II	17 (65.38)	15 (55.56)	0.002
III	7 (26.92)	0 (0.0)	
IV	0 (0.0)	4 (14.81)	
Stage			
III	11 (42.31%)	13 (48.15)	0.63
Iva	15 (57.69%)	14 (51.85)	

According to the AJCC 2010 staging system: In group A, 42.31% of the included patients had stage III and 57.69% had stage IVa, while for group B: 48.15% of the patients had stage III and 51.85% had stage IVa. T stage of the primary tumor was balanced between both groups. For group A, 10 out of 26 patients (38.46%) had T3 tumors, eight patients (30.77%) had T4 tumors, and 8 patients (30.77%) had T1 and T2. For group B, 11out of 27 patients (40.74%) had T3 tumors, eight patients (29.63%) had T4 tumors, and 8 patients (29.63%) had T2 tumor with no patient in this group had T1. In group A: 16 out of 26 patients (61.54%) had N2 disease, five patients (19.23%) had N1, 5 patients had negative lymph nodes, and no patient had N3. In group B: 11out of 27 patients (40.74%) had N0 disease, nine patients (33.33%) had N1, 6 patients (22.22%) had N2, and one patient (3.71%) had N3. Overall, the tumor stage was balanced between both groups except for nodal status, which was significantly different with tendency to higher nodal stage for the tested regimen (group A) table (2).

3.2. Tumor Grade

There was statistically significant difference between the pathological grade distributions in the two groups. In group A, 2 patients (7.69%) had had Grade 1 tumors, 17 patients (65.38%) had grade II, and 7 patients (26.92%) had grade III and no patient had grade IV tumor. In group B, 8 patients (29.63%) had Grade 1 tumors, 15 patients (55.56%) had grade II, 4 patients (14.81%) had grade IV and no patients had Grade III tumor table (2).There was statistically significant difference between the two groups as regards pathological grade.

3.3. Overall Treatment Time

After exclusion of the seven patients mentioned previously, the median overall treatment time for group A was 8 weeks, it ranged from 7 to 10 weeks, while the median overall treatment time for group B was 7 weeks, it ranged from 7 to 9 weeks. In group A, ten patients ended their treatment with no interruption, while 16 patients had treatment interruption due to severe toxicity mainly mucositis (in 8 patients), patient factors and breaks in our linear accelerator (in 8 patients). In group B, 17 patients ended their treatment with no interruption while ten patients had their interruption due to toxicity mainly dysphasia, patient factors and breaks in our linear accelerator.

3.4. Treatment Response

All patients (53) were evaluated two months after the end of treatment. All patients showed an objective response, either complete or partial response. There was no statistically significant difference between both groups as regards objective response rates. The median duration of response in group A was 21 months (range 4-30), while in group B it was 23 months (range 10-30) table (3). There was no statistically significant difference between both groups as regards response at 6, 12, 18 and 24 months.

Table (3). *Response 2 months after the end of treatment:*

Response	Group A	Group B	P value
2 months after end of treatment	No (%)	No (%)	
CR	20 (76.92%)	21 (77.78%)	0.94
PR	6 (23.08%)	6 (22.22%)	

In group A, six patients had PR to primary treatment and one relapsed after CR. Four patients received palliative chemotherapy, and three underwent salvage surgery. In group B, six patients had PR. Two patients underwent salvage surgery, and four patients received palliative chemotherapy.

3.5. The Effect of Different Prognostic Factors on Response

Group A: No statistically significant effect of sex, age and performance status on response. No statistically significant effect of primary tumor site, stage and pathological grade on response. There was a trend for better response for patients with T2 or pathological grade II.

Group B: No statistically significant effect of sex, age and performance status on response. No statistically significant effect of primary tumor site, stage and nodal status on response. There was a trend for better response in patients with laryngeal cancer. No statistically significant difference between the two groups (A&B) as regards response by sex, age, primary tumor site, stage, nodal status, pathological grade, performance status.

3.6. Survival

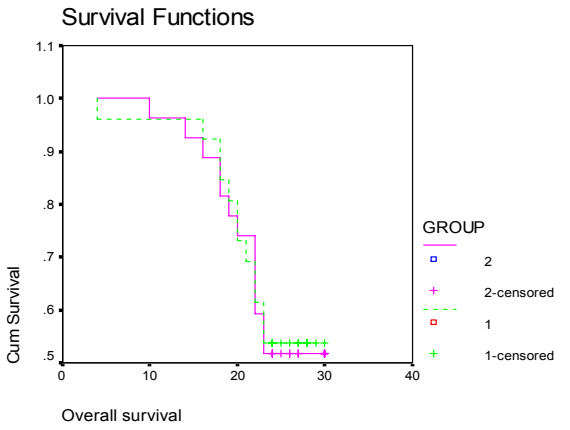
At a median follow-up of 24 months, there was no statistically significant effect of primary tumor site, disease stage, nodal status or response on survival in the group A patients. But there was a statistically significant effect of primary tumor site on survival in group B patients. This was evident in laryngeal cancer patients who showed better survival than those with other primaries. After correlation between the primary tumor site and other prognostic factors, the primary tumor site had an insignificant effect on survival. Disease stage and nodal status had no statistically significant effect on survival in group B patients. The degree of response had a statistically significant effect on survival in group B patients. This was evident in patients who achieved partial response (PR) that showed lower survival than those with (CR). After correlation between the response and other prognostic factors, response had an insignificant effect on survival. Table (4) and Table(5) Fig(1-3).

Table (4). *survival parameters in both groups*

Characteristics	Group A	Group B	P value
OAS			
Mean (SD)	22.85 (±5.33)	23.41 (±5.28)	0.75
Median (range)	24 (4-30)	24 (10-30)	
PFS =TTP			
Mean (SD)	21.54 (±5.93)	22.15 (±5.40)	0.77
Median (range)	21 (4-30)	23 (10-30)	
DFS			
Mean (SD)	16.58 (±10.89)	18.52 (±10.66)	0.50
Median (range)	20 (0-30)	23 (0-30)	

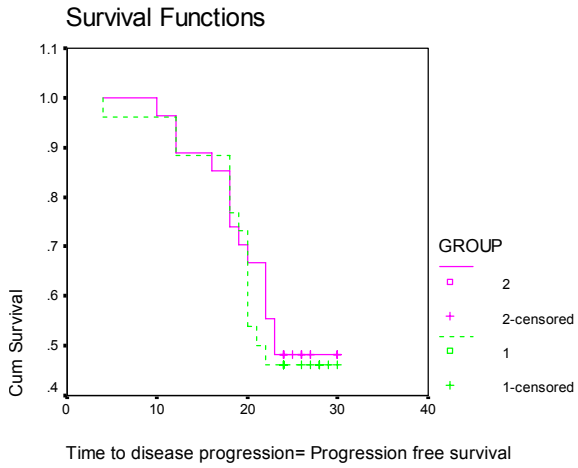
Table (5). *2 years Survival parameters in both groups*

Characteristics	Group A	Group B
2 year OAS	54%	52%
2year PFS	46%	48%
2year DFS	38%	44%



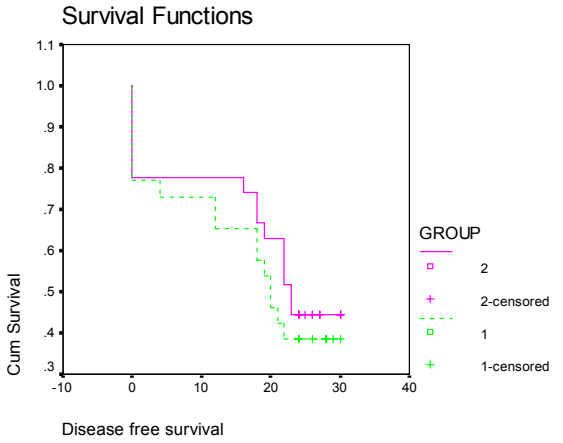
P value = 0.90, Group 1(A), Group 2(B)

Fig (1). *Overall Survival*



P value = 0.82, Group 1(A), Group 2(B)

Fig (2). *Progression Free Survival*



P value = 0.49, Group 1(A) , Group 2(B)

Fig (3). *Disease Free Survival*

3.7. Treatment Related Toxicity

Acute and late toxicities were recorded according to RTOG scoring system.

Acute skin reactions: Acute skin reactions were experienced by 92.3% of the group A patients and 92.6% of group B patients. The maximum grade of toxicity was grade 3 which was experienced in one patient only of group A (3.85%). The most frequent grade of skin toxicity was grade 1 which was experienced in 16 patients (61.54%) of group A and in 21 patients (77.78%) of group B. There was no statistically significant difference between the acute skin toxicities in the two groups.

Acute mucositis: Acute mucositis was experienced by all patients of group A and by 24 patients (88.89%) from group B. The high grades of acute mucositis (grade 3 and 4) were frequently experienced in patients of group A (77% of patients). While the low grades were experienced more frequently in patients of group B. There was a statistically significant difference between acute mucositis in the two groups.

3.8. Acute Upper Gastrointestinal Tract Toxicity

As regards nausea there was a statistically significant difference between the two groups. Grades 2 and 3 were more pronounced in the group A patients (26.92%) while patients of group B experienced mainly grades 0 and 1. As regards vomiting there was no statistically significant difference between the two groups. There is a trend for statistically significant difference between the two groups as regards acute dysphagia which was higher for group A. (P value= 0.06). There was no statistically significant difference between the two groups as regards acute hematologic, hepatic and renal toxicities.

Chronic toxicities: Xerostomia. There was a statistically significant difference between the two groups as regards xerostomia (P value= 0.013). Where no xerostomia was experienced in ≈ 70% of group B patients and xerostomia grade 1 was more pronounced in the group A patients. There was a statistically significant difference between the two groups as regards chronic mucosal toxicity (P value= 0.009). Where chronic mucosal affection grades 2 and 3 were experienced in patients of group A only (26.92%), while grades 0 and 1 were the only grades encountered in group B patients. Chronic skin and subcutaneous toxicity: there was no statistically significant difference between the two groups as regard chronic skin and subcutaneous toxicity. Our study was designed to test the efficacy and toxicity of weekly low dose gemcitabine concurrent with radiation compared with a control regimen of cisplatin concurrent with radiation in a group of patients with locally advanced HNSCC. We found that the tested regimen showed a nearly equal tumor response rate and survival results in comparison with the control regimen. Xerostomia and mucosal toxicity either acute or chronic were significantly higher for the tested regimen in comparison to the control arm. Even that in our study we used gemcitabine at a lower dose (50 mg/m2), to decrease mucosal toxicity as documented by some studies (7).

4. Discussion

In our study the complete response and partial response rates (2 months after the end of treatment) were 76.9% and 23.1% respectively in gemcitabine group which was not different than cisplatin group (77.8% and 22.2%) . This was higher than the results obtained by Eisbruch et al. (1997) who conducted a phase II trial, testing the treatment of locally advanced HNSCC with low dose gemcitabine based concurrent chemo-radiation. The response rate was 66–87% among the various cohorts. Our study response rates were higher than that obtained by Ali and Abdelraheem, 2011,who found that the response rate was 88.5% in 52 patients after receiving concurrent radiotherapy (70 GY/7 weeks) and gemcitabine (50mg/m2/weekly) (8). Aguilar et al. (2004) conducted a study which included 27 patients treated by radiation therapy 70 Gy with concurrent gemcitabin 100mg/m2/week, and achieved complete and partial response rates of 61% and 27% respectively. This difference could be due to the fact that, the included patients in the previous two trials had a relatively higher tumor stages than our study. Shaharyar et al. (2006) conducted a study including thirty-nine patients with stage III or IVB inoperable carcinoma of head and neck. Gemcitabine 150mg/m2 or a total dose not exceeding 200 mg was given weekly during radiation. Radiation was delivered with conventional fractionation to a total dose of 66-70Gy. They obtained a partial response rate of 71.4% and complete response rate of 22.9 %. This is slightly lower than overall response in our study with reversed rates of partial response and complete response, despite using gemcitabine dose three times higher than the dose in our study. This may be because they excluded the good prognostic sites (nasopharyngeal, laryngeal cancer) (9). Sirisinha et al. (2006) conducted a study which included 24 patients of primary stage III/IV head and neck cancer. RT was given at 65–70 Gy over 6.5–7 weeks concurrently with 7 weekly Gemcitabine at 4 dose levels (30 mg/m2, 50 mg/m2, 60 mg/m2 or 75 mg/m2). Nineteen patients (83%) responded, 9 patients (40%) achieved complete response (CR), 10 patients (43%) achieved partial response (PR) and 3 patients had stable disease (SD) (10). In other trial, at the same geographic area of South Egypt, conducted by Mohamed Sonosy et al. (2007) forty patients with locally advanced, stages III and IV non metastatic head and neck squamous cell carcinoma (HNSCC) were enrolled, including oropharynx, hypopharynx, and larynx. They received concurrent chemoradiotherapy using gemcitabine 100mg/m2/week given weekly throughout the radical conventional radiotherapy course of 70 Gy over 7 weeks”., overall response rate was 70%. Out of the 40 patients CR was achieved in 20 patients (50%) and PR in 8 patients (20%). Seven patients (17.5%) had progressive disease and 5 patients (12.5%) had disease. The response rates were

lower than that of our study, despite the use of double the dose of gemcitabine used in our trial (11). Ashok Chauhan et al. (2008) conducted a trial in which 80 histopathologically proven squamous cell head and neck carcinoma cases were included. They were randomly assigned to receive radiotherapy alone or to gemcitabine along with radiotherapy. The rates of complete and partial responses were 42.5% & 57.5% for RT only, and 62.5% &37.5% for CT/RT group respectively. There was no significant difference in the response rates (12).As regards to treatment related toxicity, when we compare the toxicity of the gemcitabine containing arm to other studies used the same drug. Aguilar et al. (2004) reported that, severe mucositis (grade 3–4) was observed in 74% of patients (grade 4, 41%). Severe hematological toxicity was uncommon. Mild and moderate xerostomia were the most common late toxicities in 23 patients (85%). In our study, severe mucositis (grade 3–4) was observed in 77% of patients of the tested group (grade 4, 30.7%), no severe hematological toxicity was observed. Mild and moderate mucosal toxicity was the most common late toxicity in 89% of patients of gemcitabine group followed by mild and moderate xerostomia which affected 69% of patients in this group. This was comparable to that of Eisbruch et al. 1997 (13), Aguilar et al. 2004 (7) and Ali and Abderaheem. 2011(8).In Shaharyar et al. study(2006), Grade 3 mucositis was seen in 28 patients (71.8%) grade 4 mucositis was seen in 2 patients (5.1 %). and grade 3 was documented in 6 patients (15.4%), while grade 2 toxicity was seen in 12 patients (30.8%). Acute toxicities led to treatment interruption in 40% of the included patients (9). In Mohamed Sonosy et al. (2007) study, all patients developed some degree of mucositis, with grade 3 and 4 reported in 55% of patients, which is lower than what we documented in our study (11). Ashok Chauhan et al. (2008) reported severe mucositis reactions in 67% patients in the CT/RT group vs 16% of patients in the RT only group, which were lower than that of our study. No severe hematological toxicity was seen (12).At a median follow-up time of 24 months (range 4-30) for the gemicitabine group in our study, 2-year overall survival (OS), 2-year progression-free survival and 2-year disease-free survival were 53.84%, 46.15% and 38.46% respectively and this result was in agreement with Ali and Abdelraheem, 2011 (8). In Aguilar et al. study, at a median follow-up of 13 months (range 6–62), the actuarial 3-year progression-free survival (PFS) and overall survival (OS) were 37% and 33%, respectively. The only variable associated with prolonged survival (P = 0.0001) was the degree of response. These results were lower than our study. This could be explained by the longer range of follow up their study (upper limit was 62 months versus 30 months in our study). In addition in our study the response had no statistically significant effect on survival (7). In a trial conducted by R.Sharma et al. published in conjunction with the 2008 ASCO annual meeting, they compared two regimens of concurrent chemoradiation in locally advanced head and neck cancers (weekly paclitaxel compared with cisplatin-based regimen). The median duration of follow up was 12 months in each group (range 3-53 months). In the paclitaxel arm, 43 (74.13%) patients remained alive and disease-free, whereas in the cisplatin arm, 33 (67.34%) patients were alive disease-free. This difference was not statistically significant (p=0.34). The 2-year locoregional relapse free survival was 60% in the Paclitaxel arm and 52% in the Cisplatin arm. The DFS and Two-year PFS results were higher (better) than our results in both groups. For the Cisplatin arm in their study compared to the same arm on our study, 2-year PFS was 52% versus 48% respectively (14). Three randomized trials established the use of cisplatin-based chemoradiotherapy. The trial reported by Adelstein et al. (2003) randomized 295 patients with unresectable locoregionally advanced disease to one of three treatment groups: 70 Gy radiation administered in conventional daily 2 Gy fractions, the same radiotherapy regimen with 100 mg/m2 of cisplatin concurrently on days 1, 22, and 43 during radiotherapy and a split course of radiation with doublet chemotherapy. At a median follow-up of 41 months, the single-agent cisplatin-based chemoradiotherapy was significantly more efficacious, increasing the overall survival at 3 years (37% for concurrent chemoradiotherapy versus 23% for radiation alone) (15). Where as in our study the OAS at 2 years was 54% and 52% (in gemcitabine and cisplatin arms respectively). Two other trials of cisplatin-based chemoradiotherapy compared with radiation were reported. The first study, included patients with advanced Laryngeal Cancer. It was done by Forastiere AA et al., 2003.The median follow-up period was 3.8 years. At two years, the proportion of patients who had an intact larynx after radiotherapy with concurrent cisplatin (88 %), differed significantly from the proportions in the groups given induction chemotherapy followed by radiotherapy (75%), (P=0.005) or radiotherapy alone (70 %) (P<0.001). The rate of locoregional control was also significantly better with radiotherapy and concurrent cisplatin (78 percent, vs. 61 percent with induction cisplatin plus fluorouracil followed by radiotherapy and 56 percent with radiotherapy alone).Two-year and five-year estimates of overall survival did not differ significantly according to the treatment. Patients who received chemotherapy had significantly improved disease-free survival as compared with those who received radiotherapy alone (16).The second study was done by Al-Sarraf M et al. 1998.They reported that in patients with advanced nasopharyngeal cancer. The median progression-free survival (PFS) time was 15 months for radiotherapy arm and was not reached for the chemo-radiotherapy group. At 3-year PFS rate was 24% versus 69%, respectively (P < .001). The survival rate was 47% versus 78%, respectively (P = .005). These results were better than our results, this may be explained by the fact that the primary tumor sites in our study included many primaries with poor prognosis (hypopharynx and tongue base) compared to relatively better prognosis for naso pahryngeal and laryngeal cancer included in their

studies(17). Taxanes were reported to be a potent radiosensitizer. Some studies have examined single-agent paclitaxel-based chemoradiotherapy in locally advanced HNSCC (Sanchiz F et al., 1990) (18). One phase II study used 2 mg/m2 paclitaxel three times weekly during radiotherapy in patients with poor performance status. A response rate of 65% and 2-year survival of 46% were reported (Lovey J et al., 2003) (19). Furthermore, a dose-escalation study done by Pergolizzi S et al., 2004, showed that paclitaxel was tolerated with radiotherapy when administered at weekly doses of up to 40 mg/m2. Mucositis and leukopenia were reported, but these toxic effects were generally predictable and manageable (20). The response rate in our study was better than that of Lovey J et al.(2003) and our 2-year survival was higher (54% and 52% versus 46%). Docetaxel was studied in a phase II trial done by Calais G et al., 2004 at a dose of 20 mg/m2 weekly with standard radiation therapy. They reported a 3-year overall survival of 47%. The main side effects were grade 3 or 4 mucositis (84%) and grade 3 or 4 skin toxicity (53%). By contrast, hematologic toxic effects were infrequent. Only 5% of patients experiencing grade 3 or 4 neutropenia (21). The results of this study regarding survival and toxicity profile are comparable with our results. In 2006, Adelstein et al. published the results of a study of cisplatin and 5-FU with conventional once-daily or twice-daily radiotherapy. They reported (65.7%) 5-year overall survival. Mucositis (grade 3 or 4, 40–98%), haematologic toxic effects (grade 3 or 4, 30–40%), and renal dysfunction (in up to 5% of patients) were noted .Overall survival in this study was better than of ours with a comparable percentage of mucositis but higher rates of high grade hematological toxicity (22).Several multi-agent chemoradiotherapy regimens were compared in the RTOG 97-03 multicenter randomized, phase II trial. Patients received cisplatin and paclitaxel chemoradiotherapy, cisplatin and 5-FU chemoradiotherapy or 5-FU and hydroxyurea chemoradiotherapy (FHX). This trial demonstrated equivalent 2-year overall survival for cisplatin / paclitaxel chemoradiotherapy and the FHX regimen (66.6% and 69.4%), and both of these regimens were superior to cisplatin/ 5-FU chemoradiotherapy (57.4%). Two-year overall survival for the first two regimens were better than that of our results, while the 2-year overall survival result of the last regimen (cisplatin and 5-FU chemoradiotherapy) was comparable to our results (23).Carter et al. (2003) reported a trial of 52 patients with stage III or IV unresectable HNSCC who were treated with weekly carboplatin (area under the curve = 1) and paclitaxel (40 mg/m2) in combination with hyperfractionated radiotherapy. 2-year survival was 63%. Acute grade 3/4 toxic effects were reported in 80% of patients, and these side effects were generally manageable. Two-year overall survival was comparable to our results, with more acute grade 3/4 toxicities (24). Two European trials examined the use of carboplatin and 5-FU-based chemoradiotherapy. In the first trial, 226 patients with locally advanced oropharyngeal cancer were randomized to receive radiation or concurrent chemoradiotherapy. The group receiving the combined regimen had significantly higher 3-year survival than those receiving radiation alone (51% versus 31%) and an improved locoregional control rate (66% versus 42%) (25). In another trial, 240 patients with unresectable stage III or IV oropharyngeal and hypopharyngeal cancers were randomized to hyperfractionated accelerated radiation alone or combined with carboplatin and infusional 5-FU. Overall survival at one year for the combined treatment group improved from 44% to 58%. Acute radiation-related toxicities included (grade 3 or 4 mucositis 68%, dermatitis 30%, and neutropenia 18%) (26).The first trial showed comparable survival results with our trial in the combined regimen arm, but with lower response rates. While the second trial result was comparable to our study, in both survival and toxicity profile.

5. Conclusion

Gemcitabine has a comparable radiosensitizing effect with an acceptable toxicity, and can be used as a radiosensitizer in head and neck cancers especially when cisplatin cannot be used. Further studies are recommended to establish its rule.

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