Original Article

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Clinical benefits of concurrent capecitabine and cisplatin *versus* concurrent cisplatin and 5-flurouracil in locally advanced squamous cell head and neck cancer

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ABSTRACT: We aimed to assess the efficacy and safety of concurrent capecitabine and cisplatin over concurrent cisplatin and 5-flurouracil (5-FU) in locally advanced squamous cell carcinoma of the head and neck. One hundred and fifty-three patients (all of whom had stage III or IV unresectable disease with no distant metastases and who had received two cycles of taxol and cisplatin chemotherapy) were randomly assigned to receive either concurrent cisplatin (75 mg/m^2 in day 1 and 2) and 5-FU (750 mg/m^2 in day 1, 2, and 3) from the first day of radiotherapy at an interval of 3 weeks (Arm I) or cisplatin (75 mg/m^2 in day 1 and 2) and capecitabine (750 mg/m^2 in two divided doses from day 1-14) from the first day of radiotherapy at a 3-week interval (Arm II). Results showed that patients in Arm II had a significantly better rate of complete response, fewer nodes, and better overall response compared to those in Arm I. The two groups had a similar 3-year disease-free survival, progression-free survival, and overall survival, *i.e.* they did not differ significantly. Variables indicating the quality of life of the two groups were compared. Patients in Arm II had a significantly higher quality of life compared to those in Arm I. The two groups had similar treatment-related acute and late toxicity, *i.e.* they did not differ significantly. These results have thoroughly substantiated the contention that concurrent chemoradiation with capecitabine and cisplatin may be regarded as an effective and well-tolerated regimen in the treatment of the patients with locally advanced head and neck cancer.

Keywords: Head and neck cancer, capecitabine, chemoradiation

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1. Introduction

Most patients with squamous cell carcinoma of the head and neck present with loco-regionally advanced disease, which is associated with a poor prognosis despite all available treatment (*1*). Since the treatment has additional effects on functional abilities, such as speech and eating in these patients, recent attempts to improve the major end points of treatment (local control, organ preservation, and overall survival) have focused on the use of concurrent chemoradiation (*2-7*). Cisplatin combined with 5-flurouracil (5-FU) has been considered a standard regimen for concurrent chemoradiation (*3-5*). However, 5-FU has adverse effects such as oral mucositis, which is an additive complication of radiation, and myelosuppression; the adverse effects can result in treatment-related hospitalization or mortality, thereby diminishing quality of life and reducing compliance to treatment (*4,7*).

Therefore, a chemoradiotherapy regimen with reduced toxicity but maintained efficacy is needed. Oral fluoropyrimidine capecitabine was rationally designed to preferentially generate 5-FU in tumor tissue and mimic continuous-infusion 5-FU. This tumor selectivity is achieved by exploiting the significantly higher activity of thymidine phosphorylase (TP) in many tumor tissues compared to healthy tissue, thus reducing toxicity when used as a radiosensitizer (*8*). The expression of this enzyme is enhanced in tumor areas with poor perfusion, hypoxia, and acidosis; this situation is found in most advanced head and neck squamous cell carcinoma. There is evidence that radiation leads to the upregulation of thymidine phosphorylase expression, thereby synergizing the action of capecitabine (*9*). Mounting evidence suggests that oral capecitabine, which mimics continuous 5-FU infusion, has substantial activity in squamous cell carcinoma of the head and neck (*10,11*) and is replacing 5-FU in the treatment of many solid tumors as well as in advanced head and neck squamous cell carcinoma (*12-20*). Thus, the impact of radiation-induced toxicity on quality of life and treatment compliance justifies the use of concurrent chemoradiotherapy with an oral capecitabine-based regimen.

The objective of this study was to evaluate the benefits of concurrent capecitabine and cisplatin over concurrent cisplatin and 5-FU in locally advanced squamous cell head and neck cancer by assessing the response rate, survival, quality of life, and treatment-related toxicity during a three-year clinical follow up.

2. Materials and Methods

2.1. *Study protocol*

In total, 153 patients with head and neck cancer in a locally advanced stage (III, IV, M0) and a performance status of grade 1-2 seen by O.P.D from 2004-2005 were enrolled in the study. These patients were assessed thoroughly (history, clinical examination, and imaging studies) as shown in Table 1 and scheduled for treatment. All 153 patients were randomly divided to receive treatment in two arms. In Arm I, 75 patients received taxol (175 mg/m^2, day 1) and cisplatin (50 mg/m^2, day 2) administered as neoadjuvant chemotherapy in two cycles at a 21-day interval followed by concurrent chemoradiation where three cycles of cisplatin (75 mg/m^2 on days 1 and 2) and 5-FU (750 mg/m^2 on days 1, 2, and 3) at a 3-week interval along with radiotherapy at a dose of 70 Gy/35 fractions for 7 weeks. In Arm II, 78 patients received the same neoadjuvant chemotherapy regimen followed by concurrent chemoradiation with three cycles of cisplatin (75 mg/m^2 on day 1 and day 2) and capecitabine (750 mg/m^2 in two divided doses from days 1-14, with pyridoxine 200 mg in two divided doses on days 1-14) at a 3-week interval along with radiotherapy at a dose of 70 Gy/35 fractions for 7 weeks. Both arms are summarized in Table 2.

Table 1. Demographic and clinicopathological characteristics of two groups

Characteristics	Arm I (n = 67)	Arm II (n = 71)	p value
Age (years)			0.931
Mean ± SD	52.37 ± 11.10	52.54 ± 10.75	
Range	32-73	30-75	
Sex			0.380
Female	11 (16.4%)	8 (11.3%)	
Male	56 (83.6%)	63 (88.7%)	
Performance status			0.709
1	59 (88.1%)	61 (85.9%)	
2	8 (11.9%)	10 (14.1%)	
Site			0.573
Hypopharynx	14 (20.9%)	20 (28.2%)	
Larynx	22 (32.8%)	17 (23.9%)	
Oral cavity	11 (16.4%)	10 (14.1%)	
Oropharynx	20 (29.9%)	24 (33.8%)	
Histology:			0.457
Well differentiated	22 (32.8%)	17 (23.9%)	
Moderately differentiated	42 (62.7%)	49 (69.0%)	
Poorly differentiated	3 (4.5%)	5 (7.0%)	
Tumor:			0.492
T1	8 (11.9%)	4 (5.6%)	
T2	19 (28.4%)	22 (31.0%)	
T3	27 (40.3%)	34 (47.9%)	
T4	13 (19.4%)	11 (15.5%)	
Node:			0.766
N0	7 (10.4%)	6 (8.5%)	
N1	25 (37.3%)	30 (42.3%)	
N2	33 (49.3%)	31 (43.7%)	
N3	2 (3.0%)	4 (5.6%)	
Stage:			0.841
III	30 (44.8%)	33 (46.5%)	
IV	37 (55.2%)	38 (53.5%)	

Patients were evaluated 4-6 weeks after completion of treatment. The clinical benefits of concurrent chemoradiation with capecitabine and cisplatin in treating locally advanced squamous cell carcinoma of the head and neck were evaluated in terms of the response rate, 3-year overall survival and disease-free survival, radiation-induced toxicity, energy level (EL), activity level (AL), and overall quality of life (OQOL).

Informed written consent was obtained from each patient according to institutional regulations.

2.2. *Dose modification*

The protocol plan was continued despite mucositis or dermatitis. However, if grade 3 or 4 capecitabine/5-FU-related hematological or non-hematological toxicity such as mucositis, diarrhea, and hand-foot syndrome developed, capecitabine/5-FU was withheld until toxicity had improved by at least two grade levels. Subsequent capecitabine doses was reduced by 20%, doses of 5-FU was reduced by 20-25%. The dose of cisplatin was reduced to 50% if the calculated creatinine clearance level was 30-50 mL/min. No cisplatin was given if the creatinine clearance level was less than 30 mL/min. If myelosuppression (WBC count < 4,000/mm^3 or platelets count less than 100,000/mm^3) was present and a fever over 38°C or other clinically evident infection persisted, the cycle was postponed for 1 week or interrupted.

Table 2. Treatment given to two groups during the study

Treatment protocol	Arm I (n = 67)	Arm II (n = 71)
Neoadjuvant chemotherapy regimen	Taxol (175 mg/m^2, day 1), cisplatin (50 mg/m^2, day 2) × 3 weekly; 2 cycles	Taxol (175 mg/m^2, day 1), cisplatin (50 mg/m^2, day 2) × 3 weekly; 2 cycles
Concurrent chemotherapy	Cisplatin (75 mg/m^2, day 1 and 2), 5-FU (750 mg/m^2, day 1, 2, and 3) × 3 weekly; 3 cycles	Cisplatin (75 mg/m^2, day 1 and 2), capecitabine (750 mg/m^2, day 1-14) × 3 weekly; 3 cycles
	Radiotherapy, 70 Gy/35 fractions in 7 weeks	Radiotherapy, 70 Gy/35 fractions in 7 weeks

2.3. *Surgery*

Salvage surgery at the primary tumor site was recommended for eligible patients with residual disease who failed to achieve a complete response (CR) upon completion of treatment. Surgery in case of residual disease was carried out 6-8 weeks after completion of treatment.

2.4. *Study assessments*

Before starting treatment, all patients underwent a full medical history and physical examination, blood tests, computed tomography (CT) or magnetic resonance imaging (MRI) of the head and neck, and chest X-ray/CT-scan of the chest if lower neck nodes were involved.

Assessment of tumor response was done by clinical examination and imaging studies (X-rays, CT-scan) 4-6 weeks after completion of treatment. Biopsy or fine needle aspiration cytology was not routinely performed to determine pathological response; it was done only in the event of partial response/suspected lesions to confirm the presence of disease.

The definition of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) was based on the standard definitions established by the World Health Organization (1979). Patients were monitored for acute chemoradiation-induced toxicity (by medical interview, physical examination, and complete blood count) weekly during chemoradiation; late radiation toxicity was assessed during follow-up. Toxicity was graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0. Hand-foot syndrome was graded 1-3.

2.5. *Statistical analysis*

Continuous data were summarized as mean ± SD while discrete data (categorical) were indicated in %. Continuous variables were compared using an independent Student's *t* test while discrete variables were compared with a chi-square (χ^2) test. Groups were also compared by two-factor repeated measures analysis of variance (ANOVA) followed by a Bonferroni post hoc test after ascertaining normality and homogeneity of variance with a Shapiro-Wilk test and Levene's test, respectively. The survival of the two groups was compared using the Kaplan-Meier technique and the difference in the survival rate was determined with a Logrank test. A two-tailed ($\alpha = 2$) $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. *Basic characteristics*

The demographic (age, sex, and performance status) and clinicopathological (site, histology, tumor node and stage) characteristics of the two groups (Arm I and Arm II) at admission are summarized in Table 1. The age of patients in Arm I and Arm II ranged from 32-73 years and 30-75 years, respectively, with a mean ± SD of 52.37 ± 11.10 years and 52.54 ± 10.75 years, respectively. In both groups, patients were mostly male and most had a good performance status. In Arm I, the most prevalent site of the primary tumor was the larynx (32.8%); in Arm II, it was the oropharynx (33.8%). In both groups, most patients had tumors with a moderately differentiated (MD) histology; most tumors were class T3, lymph node involvement was N2, and tumors were stage IV. The two groups had similar basic characteristics, *i.e.* they did not differ significantly ($p > 0.05$).

3.2. *Treatment response*

Sixty-seven of the patients in Arm I completed the planned treatment while 71 in Arm II did so; the remaining 8 in Arm I and 7 in Arm II were lost to follow-up or patient refusal. The treatment response of the two groups was evaluated after completion of the respective treatments (4-6 weeks after completion of treatment) and after chemoradiation. Of the patients in Arm I, 36 were CRs (53.7%) and 28 were PRs (41.8%) while in Arm II 55 were CRs (77.5%) and 12 were PRs (16.9%). There were 38 (56.7%) primary and metastatic lymph node CRs and 36 PRs (53.7%) in Arm I while in Arm II there were 55 primary and metastatic lymph node CRs (77.5%) and 56 PRs (78.9%), as summarized in Table 3. Patients in Arm II had a significantly better CR, fewer nodes, and overall survival compared to those in Arm I. Furthermore, the dose reduction and treatment delay also lowered significantly in Arm II compared to those in Arm I.

3.3. *Survival*

After completion of 4-6 weeks of treatments, the two groups of patients were followed for three years. In both

Table 3. The treatment response of two groups

Characteristics	Arm I ($n = 67$)	Arm II ($n = 71$)	p value
Tumor			0.026
CR	38 (56.7%)	55 (77.5%)	
PR	26 (38.8%)	13 (18.3%)	
NR	3 (4.5%)	3 (4.2%)	
Node			0.005
CR	36 (53.7%)	56 (78.9%)	
PR	28 (41.8%)	12 (16.9%)	
NR	3 (4.5%)	3 (4.2%)	
Overall			0.006
CR	36 (53.7%)	55 (77.5%)	
PR	28 (41.8%)	12 (16.9%)	
NR	3 (4.5%)	4 (5.6%)	
Dose reduction	13 (19.4%)	5 (7.0%)	0.031
Treatment delay	16 (23.9%)	5 (7.0%)	0.006

groups, no death was observed during the treatments or end of the treatments. However, during follow up, 8 (10.6%) patients left the treatment and 13 (19.4%) died due to disease in Arm I while 7 (8.9%) and 9 (12.7%), respectively, in Arm II. Thus, at the end of the study, total 46 (68.6%) patients were found live in Arm I while 55 (77.4%) in Arm II. The 3-year disease-free survival (χ^2 = 0.89, p = 0.346), progression-free survival (χ^2 = 2.59, p = 0.107), and overall survival (χ^2 = 1.45, p = 0.229) of two groups were found similar *i.e.* did not differed significantly ($p > 0.05$) though it were 3.00 (HR = 3.00, 95% CI = 0.30-30.58)-, 2.34 (HR = 2.34, 95% CI = 0.83-6.41)-, and 1.67 (HR = 1.67, 95% CI = 0.72-3.89)-fold higher in Arm II compared to those in Arm I (Figure 1).

3.4. *Quality of life*

The changes in hemoglobin (Hb), weight, and quality of life were compared and summarized graphically (Figure 2) using 100 mm Linear Analog Scale Assessments

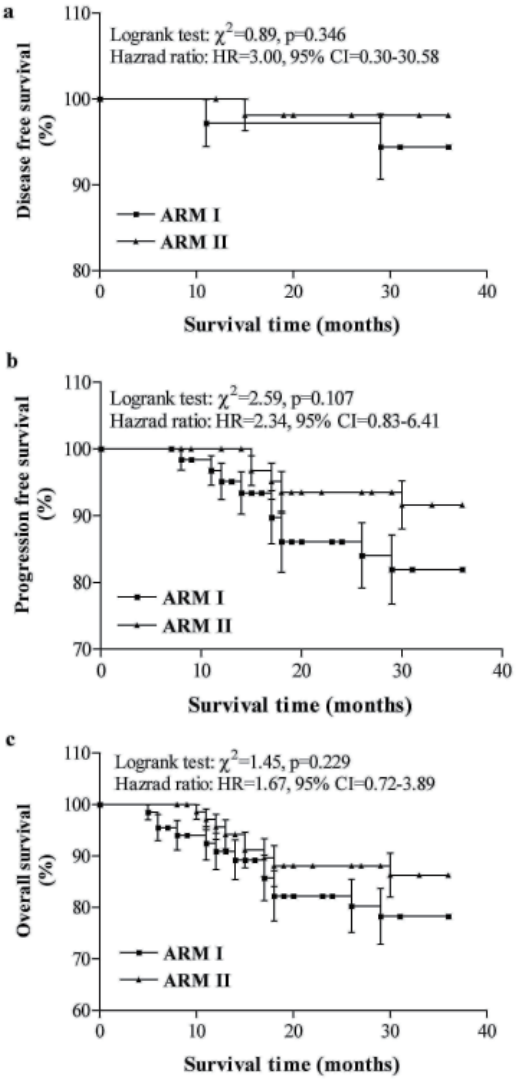

Figure 1. The 3-year disease-free survival (a), progression-free survival (b), and overall survival of two groups (c).

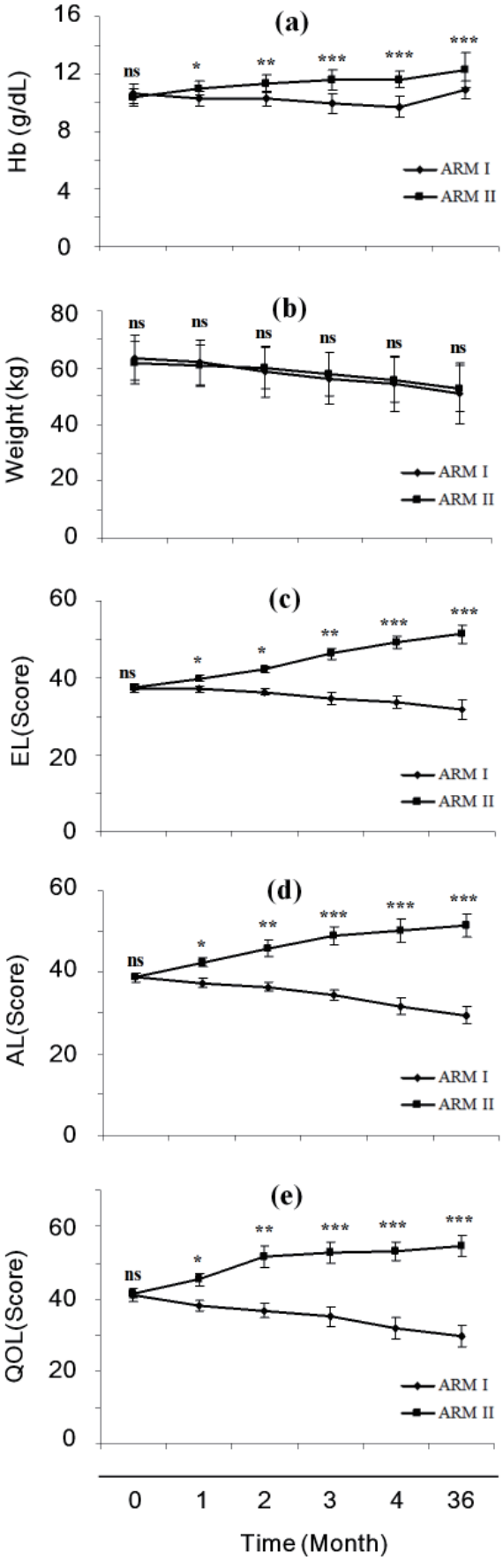

Figure 2. Improvement in Hb (a), weight (b), EL (c), AL (d), and QOL (e) for two groups. ns, $p > 0.05$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

(LASAs) that rated the EL, AL, and OQOL of the two groups during the treatments and at end of the study. Results showed that patients in Arm II had significantly better results in terms of variables compared to those in Arm I except weight. A significant difference was evident after just 1 month of treatment and was more pronounced at the end.

3.5. *Toxicity*

At the end of the treatment, the treatment-related toxicity (hematological and non-hematological) in the two groups was also compared and is summarized in Table 4. The two groups had similar treatment-related toxicity, *i.e.* they did not differ significantly ($p > 0.05$).

The most severe hematologic adverse events were neutropenia and febrile neutropenia, which occurred with grade 3/4 intensity in 20 patients (29.8%) and 6 patients (9%), respectively, in Arm I while neutropenia and febrile neutropenia were observed in 26 patients (36.6%) and 18 patients (25.4%), respectively, in Arm II. These adverse events were successfully managed, and no treatment-related deaths occurred during this study. Mucositis and dermatitis, as would be expected from a combination of radiation with an effective chemotherapeutic-sensitizing agent, were the most common form of non-hematological toxicity. Grade 3/4 mucositis and dermatitis were observed in 70.2% of patients and 25.4% of patients, respectively, in Arm I while grade 3/4 mucositis and dermatitis were observed in 53.5% of patients and 33.8% of patients, respectively, in Arm II.

4. Discussion

Chemoradiation for head and neck cancer has led to significant improvements in survival, but these improvements have come at the cost of greater incidence of oropharyngeal mucositis and hematological toxicity, which are the most common reasons for unplanned treatment interruptions. Moreover, chemoradiation regimens to treat head and neck cancer are associated with troublesome adverse events that affect nutritional status and immune status, resulting in secondary infection, treatment interruption, and dose reduction that may compromise survival and quality of life. According to the literature, 80% of patients treated with chemoradiation have grade III or

Table 4. Treatment-related toxicity in two groups

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4 (%)	*p* value
A: Hematological						
Anemia						0.323
Arm I	9 (13.4%)	13 (19.4%)	10 (14.9%)	14 (20.9%)	35.8	
Arm II	7 (9.9%)	8 (11.3%)	3 (4.2%)	3 (4.2%)	8.4	
Leukopenia						0.998
Arm I	37 (55.2%)	36 (53.7%)	21 (31.3%)	17 (25.4%)	56.7	
Arm II	26 (36.6%)	24 (33.8%)	14 (19.7%)	12 (16.9%)	36.6	
Neutropenia						0.371
Arm I	22 (32.8%)	14 (20.9%)	12 (17.9%)	8 (11.9%)	29.8	
Arm II	13 (18.3%)	11 (15.5%)	16 (22.5%)	10 (14.1%)	36.6	
Thrombo-cytopenia						0.224
Arm I	15 (22.4%)	17 (25.4%)	11 (16.4%)	11 (16.4%)	32.8	
Arm II	21 (29.6%)	9 (12.7%)	7 (9.9%)	13 (18.3%)	28.2	
Febrile neutropenia						0.147
Arm I	7 (10.4%)	5 (7.5%)	4 (6.0%)	2 (3.0%)	9.0	
Arm II	4 (5.6%)	10 (14.1%)	9 (12.7%)	9 (12.7%)	25.4	
B: Non-hematological						
Nausea						0.787
Arm I	33 (49.3%)	32 (47.8%)	7 (10.4%)	5 (7.5%)	17.9	
Arm II	39 (54.9%)	35 (49.3%)	10 (14.1%)	3 (4.2%)	18.3	
Vomiting						0.579
Arm I	31 (46.3%)	29 (43.3%)	4 (6.0%)	3 (4.5%)	10.5	
Arm II	25 (35.2%)	36 (50.7%)	6 (8.5%)	2 (2.8%)	11.3	
Renal dysfunction						0.660
Arm I	12 (17.9%)	7 (10.4%)	5 (7.5%)	3 (4.5%)	12.0	
Arm II	14 (19.7%)	5 (7.0%)	8 (11.3%)	6 (8.5%)	19.8	
Mucositis						0.365
Arm I	17 (25.4%)	33 (49.3%)	29 (43.3%)	18 (26.9%)	70.2	
Arm II	10 (14.1%)	29 (40.8%)	17 (23.9%)	21 (29.6%)	53.5	
Dermatitis						0.454
Arm I	36 (53.7%)	24 (35.8%)	11 (16.4%)	6 (9.0%)	25.4	
Arm II	31 (43.7%)	17 (23.9%)	15 (21.1%)	9 (12.7%)	33.8	
Diarrhea						0.873
Arm I	7 (10.4%)	6 (9.0%)	8 (11.9%)	5 (7.5%)	19.4	
Arm II	11 (15.5%)	13 (18.3%)	10 (14.1%)	7 (9.9%)	24.0	

IV hematological toxicity, 60% have grade III or IV mucositis, 20% have grade III or IV dermatitis, and 5% of patients die during concomitant chemoradiotherapy (*21*). Therefore newer chemotherapeutic agents that would cause less toxicity and have a high therapeutic index are needed for concurrent chemoradiation; however, no standard concurrent chemoradiotherapy regimen has been defined. Therefore, the present study was designed to evaluate the efficacy and toxicity of capecitabine instead of 5-FU in combination with cisplatin for concurrent chemoradiation to treat locally advanced squamous cell head and neck cancer.

In the current study, patients in Arm II had a significantly better CR, fewer nodes, and better overall response compared to those in Arm I, along with significant improvement in quality of life in terms of EL, AL, and OQOL. The incidence of mucositis, grade 3 or 4 neutropenia, and grade 3 or 4 febrile neutropenia differed only slightly in the two groups. However, the incidence of hematological toxicity in the current study differed significantly from that in previous studies using 5-FU-based regimens, where the incidence of grade 3 or 4 leukopenia was 29-81% (*1,18,22,23*).

Taxanes such as paclitaxel and docetaxel, which exhibit activity against squamous cell head and neck cancer, are increasingly being used in concurrent chemoradiation to improve treatment outcomes. These agents allow better locoregional control and result in better overall survival, but 34% of patients treated with the agents experienced grade 3 or 4 leukopenia and 3% patients died of treatment-related toxicity (*19*).

No hand-foot syndrome, a common complication associated with capecitabine, occurred in the patients in the current study, but the dose of capecitabine was reduced in two cycles in 5 patients due to neutropenia and mucositis and the dose of cisplatin was reduced in 13 patients because of nephrotoxicity and mucositis. The second and third cycle of chemotherapy was delayed in 16 patients (23.9%) in Arm I and 5 patients (7.0%) in Arm II due to mucositis and patient refusal to continue with the treatment.

The current study shows that although there is improvement in the response rate and quality of life in terms of EL, AL, and OQOL, there was no significant difference in survival and treatment-induced acute grade 3/4 toxicity profile. Improvement in quality of life for patients in Arm II may be attributed to a higher response rate among patients in this arm.

A number of prospective studies have also shown the efficacy and favorable safety profile of capecitabine as a radiosensitizer over other commonly used chemotherapeutic agents like cisplatin and 5-FU when treating many solid tumors, including head and neck cancer (*11-14,17,19-21,24*). The overall survival and progression-free survival rate in these studies at 2 years were 76.8% and 57.9%, respectively. Grade 3/4 mucositis and dermatitis were noted at rates of 67.6% and 24.3%, respectively. Grade 2 hand-foot syndrome, a complication of capecitabine, occurred in only 10.8% of patients. Encouraging results in terms of efficacy and the favorable safety profile of capecitabine have also been demonstrated in recent large phase-III studies comparing capecitabine with intravenous 5-FU and leucovorin to treat metastatic colorectal cancer (*18*).

Capecitabine has been widely used in the treatment of breast, stomach, and cervix cancer as well as other solid tumors (*11,13-16,19,20*). Several studies have demonstrated that concurrent chemoradiotherapy using capecitabine, with a dose ranging from 800 to 825 mg/m^2, in combination with cisplatin or oxaliplatin is effective and has a low toxicity profile in the neoadjuvant setting of rectal cancer or locally advanced esophageal cancer (*12-14*).

In conclusion, concurrent chemoradiotherapy with capecitabine and cisplatin was found to be well tolerated and effective in patients with locally advanced head and neck cancer. Accordingly, this regimen can be considered beneficial and may form an important therapeutic treatment option for locally advanced head and neck cancer, meeting the needs and assuaging the concerns of patients. However, further investigations in prospective studies with larger samples and a longer follow up are required to evaluate this regimen.

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