Phase II study of cisplatin and capecitabine plus radiotherapy in patients with locally advanced head and neck carcinoma

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Abstract

Objective: To evaluate the efficacy and safety of concurrent chemoradiotherapy with capecitabine and cisplatin in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

Patients & methods: In total, 36 patients with stage III or IV SCCHN were enrolled on the study. Chemotherapy consisted of two cycles of intravenous cisplatin of 80 mg m-2 on day 1 and oral capacitabine 825mg m-2 twice daily from 1 to day 14 at 3-week intervals. The radiotherapy (2.0 Gy/fraction day-1 to a total dose of 70 GY) was delivered to primary tumor site and neck. The primary tumor sites were as follows: oral cairty (n = 6), oropharynx (n = 10), hypopharynx (n = 8), larynx (n = 3), nasopharynx (n = 6), paranasel sinus (n = 3).

Results: At the end of chemoradiotherapy, 19 complete responses (52.8%), 14 partial responses (38.9%) were obtained. Grade 3 and 4 neutropenia occurred in two patients. At a median follow up duration of 19.8 months, the estimated 2-year overall survival and progression – free survival rate were 69.4% and 58.3% respectively.

Conclusion: Concurrent chemoradiotherapy with capecitabine and cisplatin was found to be well tolerated and effective in patients with locally advanced SCCHN.

Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for most malignancies that arise in the head & neck region (1). Two-thirds of the patients present with advanced locoregional diseases, and despite combined modality approaches with chemotherapy and radiotherapy or surgery, locoregional and distant failure occurs in up to 60% and 25% of the patients, respectively, and the 3-year survival rate remains below 30%((2). The combination of cisplatin and infusional 5-flourouracil (5FU) is a widely accepted schedule in the locally advanced or recurrent disease setting, with response rates of 60 – 80% and 30 – 40% respectively, in the latter setting, median overall survival is 6 months (3).

Generally, a combination of 5-fluorouracil (5-FU) and cisplatin has been considered as effective regimen for concurrent CRT due to the synergism between the two agents and their radiosensitizing effects (4). However, the adverse effects of 5-FU, such as oral mucositis, which is an additive complication to radiation, or bone marrow suppression, can result in treatment-related hospitalization or mortality, thereby compromising the quality of life and compliance to treatment (5,6).

The oral fluoropyrimidine (capecitabine) was rationally designed to preferentially generate 5-FU in tumor tissue and mimic continuous 5 FU (7). The convenience of oral administration of capecitabine provides an added advantage (8). The combination of capecitabine (X) and cisplatin (P) has been tested in several malignancies, including gastric, biliary and esophageal cancers (9). In addition, capecitabine has also exhibited antitumor activity when given as a monotherapy or in combination with cisplatin in patients with various solid tumours as well as in advanced HNSCC (10, 11,12).

Furthermore, since the key side effects of capecitabine are hand – foot syndrome and diarrhoea, which overlap little with the side effects of cisplatin or radiation, capecitabine can be a good chemotherapeutic agent in concurrent chemoradiotherapy (13). The current study was conducted To evaluate the efficacy and safety of concurrent chemoradiotherapy with cisplatin and capecitabine for locally advanced SCCHN.

Patients & Methods

Eligibility Criteria

This phase II study was carried out at Department of Radiation Oncology, Ain Shams university. Thirty-six patients were enrolled in this study who had measurable, histologically or cytologically confirmed, locoregionally advanced stage III or IV (SCCHN) arising from the oral cavity, pharynx, larynx or paranasal sinuses. Patients were required to have 18 years of age or older with a performance status of 0 – 2 on the Eastern Cooperative Oncology Group (ECOG) scale, adequate haematological, hepatic and renal function (WBC count ≥ 4 × 109 1-1, platelet count ≥ 100 × 109 1-1, haemoglobin ≥ 9 gd1-1 , AST or ALT levels of ≤ 3 times the upper limit of normal range, total bilirubin ≤ 2.0 mg d1-1 and a creatinine clearance ≥ 50 ml min-1).

Patients were ineligible if they had previously received radiotherapy or chemotherapy, or had other severe medical illness, distant metastasis, another active malignancy. Patients were required to provide written informed consent prior to enrolment into the study.

All patients had a complete clinical history, physical examination, complete blood counts, serum biochemistry (liver and renal function tests, and electrolytes), urinalysis and electrocardiogram. Computed tomography (CT) scan of the head and neck was done before study entry.

Treatment plan

Treatment considered of cisplatin (80mg m-2 as a 30min i.v. infusion on day 1), followed by capecitabine (825 mg m-2 orally twice daily, on days 1 – 14), every 21 days. Standard mannitol and i.v. pre- and post hydration accompanied cisplatin administration. Prophylactic antiemetics included i.v. ondansetron (8 mg) prior to chemotherapy.

Treatment was administered on an outpatient basis. Two cycles of chemotherapy was delivered every 3 weeks.

Radiotherapy (1.8 – 2.0 Gy, fraction day-1 for a total dose of 70 Gy), administered 5 days per week, was delivered to the primary tumor site and neck. Radiotherapy begins on the first day of chemotherapy. Patients underwent a complete dental evaluation and treatment as early as possible before the initiation of radiotherapy.

Dose modification

Capecitabine was withheld until the toxicity had improved by at least two grade levels if grade 3 or 4 capecitabine related hematological or nonhematological toxicity, such as diarrhoea & hand- foot syndrome, occurred. Subsequent capecitabine doses then required a 20% dose reduction. The dose of cisplatin was reduced to 50% if the calculated creatinine clearance level was 30–50 ml min^{-1}. No cisplatin was administered if the creatinine clearance level was less than 30 ml min-1. In the presence of myelosuppression (WBC count < 4×10^9 1^{-1} or platelet 38 °C, or other clinically apparent infections, a cycle could be postponed for 1 week or interrupted if it was necessary.

Surgery

Salvage surgery of the primary tumor site was recommended for operable patients, who failed to achieve a complete response (CR) at the end of chemoradiotherapy. The extent of surgery varied, ranging from laser resection or a wide excisional biopsy to a complete resection of tonsillar primary. A modified neck dissection could also be performed. The surgery was carried out routinely 6–8 weeks after chemoradiotherapy.

Study assessments

All patients underwent a full history, physical examination blood tests, computed tomography (CT) of head and neck, and chest x–ray (CT chest if the patient's low neck nodes were involved). Assessment of the tumor response by clinical examination and CT scanning took place 6 weeks after completing the chemoradiation therapy.

The definition of CR, partial response (PR), stable disease (SD), and progressive disease (PD) were based on the standard definitions established by the WHO (1979). The patients were monitored for toxicity throughout the treatment. Complete blood counts & chemistry were performed every week till the end of chemoradiotherapy. Systemic toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI – CTC) version 3.0. Acute radiation toxicities were graded according to the European Organization therapy Oncology Group (EORTC – RTOG) toxicity criteria. Hand – foot syndrome was graded 1 – 3, as defined in previous capecitabine clinical studies (14).

Study end points

The primary end point of the current study was response rate, while toxicity, progression and overall survival were the secondary end points.

Statistical analysis

Progression – free and overall survival analyses were all estimated using the Kaplan – Meier method. Time to progression was measured as the time from begining of therapy until death due to disease or toxicity, appearance of new lesions, or a greater than 25% increase of the indicator lesions over the previous smallest size. Overall survival was measured from the beginning of therapy to the date of last follow-up or any cause of death.

The statistical data were obtained using an SPSS software package (SPSS 11.0 INC. Chicago, IL, USA).

Results

Patient characteristics

In the current study, 36 patients were enrolled from February 2007 to March 2008 at Department of Radiation Oncology, Ain Shams University. The patients> characteristics are summarised in table 1. The median age of the patients was 51.0 years (range, 35 – 65 years), and 31 (86.1%) patients were male. Most of the patients 32 (88.9%) had a good performance status (ECOG 1). The primary sites of the tumors were as follows: oral cairty (n = 6), oropharynx (n = 10), hypopharynx (n = 8), larynx (n = 3), nasopharynx (n = 6), and paranasal sinus (n = 3). A total of 23 patients (63.9%) had a stage III diseases, while the remaining 13 patients were stage IV.

Response and survival

Of the 36 patients, 34 (94.4%) completed the planned treatment, with the remaining two being lost to follow up. After the chemoradiotherapy, 19 CRs (52.8%) and 14 PRs (38.9%) were confirmed, giving an overall clinical response rate of 91.7%. The primary site CR was 51.5% (17 out of 33) and metastatic lymph node CR was 48.3% (14 out of 29) (Table 2). Among the seventeen patients who failed to achieve CR after the chemoradiotherapy, eight patients underwent surgery and seven patients received salvage chemotherapy. At the time of the present evaluation, 13 patients had developed disease progression or recurrence (five – primary tumor, three – regional lymph node, two – both primary and regional lymph node and three – distant metastases to the bone) and eleven patients had died of disease progression. At a median follow up duration of 19.8 months, the estimated 2-year overall survival and progression – free survival rate were 69.4% and 58.3% respectively.

at 2 year were 69.4% and 58.3% respectively (Fig 1 & 2).

Toxicity

All 36 patients were assessable for toxicity. The hematologic and nonhematologic toxicities that occurred during the current study are summarized in Table 3. The most severe hematologic adverse event was neutropenia which was observed in two patients (5.5%).. Although this case was successfully treated with antibiotics and G-CSF, the patient refused to complete the planned treatment. No treatment-related death occurred during this study. Mucositis and dermatitis were the most common non hematological toxicities. Grade 3/4 mucositis and dermatitis was observed in 66.6 & 25%, respectively. Grade 2 hand – foot syndrome, a complication of capecitabine, occurred only in four patients 11.1%. The dose of capecitabine was reduced in two cycles due to neutropenia or diarrhoea, and cisplatin omitted from one cycle due to nephrotoxicity.

The second cycle of chemotherapy was delayed in nine patients for the following reasons: hematological toxicity (n = 7), persistent fever (n = 1), and patient refusal (n = 1). The dose intensity of capecitabine and cisplatin was well maintained throughout the study cycles.

Discussion

Concurrent chemoradiotherapy & induction chemotherapy have been established as an appropriate standard of care for patients with locally advanced SCCHN. However, no standard concurrent chemoradiotherapy regimen has been defined. Therefore, the present phase II study was designed to evaluate the efficacy and toxicity of capecitabine instead of 5FU in combination with cisplatin for concurrent chemoradiotherapy in patients with locally advanced SCCHN. In the current study, the clinical CR rate (52.8%), progression-free survival rate (58.3% at 2 yrs), following treatment with the present study, which can be administered on an outpatient basis, were nearly similar with previous results reported for 5FU and platinium based concurrent chemoradiotherapy(15,16).For example, concurrent chemotherapy with infusion of 5FU and cisplatin arm achieved a CR rate of 49.4% and 3-year overall survival rate of 27% in a randomised study compared with concurrent chemoradiotherapy (single agent cisplatin) with radiation therapy alone (17).

Since the efficacy and favorable safety profile of capecitabine have been clearly demonstrated in recent large phase III studies comparing capecitabine with intravenous 5-FU plus leucovorin for metastatic colorectal cancer (16), capecitabine has been widely used in the treatment of breast cancer, stomach cancer and other solid tumors (14,18,19).In the current study,daily administration of Capecitabine acted as chemoradiosensitister for radiotherapy.

Capecitabine is activated by TP and concentrated by radiotherapy within tumor cells, leading to better tumor control. Given these advantages, several studies have demonstrated that concurrent chemoradiotherapy using capecitabine, with a dose ranging from 800 to 825 mg m-2 b.i.d, in combination with cisplatin or oxaliplatin is effective and has a low toxicity profile in the neoadjuvant setting of rectal cancer or locally advanced oesophageal cancer (20, 21).

The most serious complications of concurrent chemoradiotherapy for SCCHN are oral mucositis and myelosuppression leading to reduced compliance to treatment or sometimes mortality. In the present study, mucositis was the most common adverse event observed, with a grade 3 or 4 intensity in (66.6%) of the patients. In a randomised study(4), the incidence of grade 3 and 4 mucosits in concurrent chemoradiotherapy with 5-FU and cisplatin was 71%, which was higher than with radiotherapy only (39%). The incidence of mucositis was not so different between chemoradiotherapy with capecitabine / cisplatin and 5-FU / cisplatin. Grade 3 or 4 neutropenia occurred only in three patients (8.3%), plus grade 3 febrile neutropenia was observed in one patient (2.8%) in the current study. These incidences of hematologic toxicities were significantly different from previous studies using 5-FU containing regimes, where the incidence of grade 3 or 4 leucopenia was 29 - 81% (16, 22). Docetaxel (Taxotere, Sanofi-Aventis) has substantial activity when administered alone in patients with recurrent or incurable disease (23). In phase 1 and 2 studies of docetaxel plus cisplatin and fluorouracil (TPF) in the treatment of locally advanced squamous-cell carcinoma of the head and neck, clinical ,pathological response and survival rates have been high (24).Therefore, taxane based regimens should be tested in a randomized trial and compared with standard concurrent regimen.

In conclusion, concurrent chemoradiotherapy with capecitabine and cisplatin was found to be well tolerated and effective in patients with locally advanced SCCHN. Accordingly, this regimen can be regarded as an important chemoradiotherapy option for advanced HNSCC, although larger studies and long-term follow-up is needed to better evaluate the safety and toxicity of this combination.

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Tables

Table 1: Patient characteristics

Characteristics	No. of patients, N = 36 (%)
Age (years)	
Median (range)	51 (35 – 65)
Male / female	31 (86.1) / 5 (13.9)
ECOG performance status	
1	32 (88.9)
2	4 (11.1)
Site of primary tumor	
Oral cairty	6 (16.7)
Oropharynx	10 (27.8)
Hypopharynx	8 (22.2)
Larynx	3 (8.3)
Nasopharynx	6 (16.7)
Paranasal sinus	3 (8.3)
Histologic classification	
Well differentiated	7 (19.4)
Moderated differentiated	10 (27.8)
Poorly differentiated	11 (30.6)
Undifferentiated	8 (22.2)
Stage	
III	23 (63.9)
IV	13 (36.1)
T classification	
T_1	3 (8.3)
T_2	14 (38.9)
T_3	13 (36.1)
T_4	6 (16.7)
N classification	
N_0	7 (19.4)
N_1	13 (36.1)
N_2	15 (41.7)
N_3	1 (2.8)

Table 2: Tumor response (intent-to-treat analysis, N = 36)

	Response (%)				
Variable	CR	PR	SD	PD	Response rate
Primary site	17/33 (51.5)	12/33 (36.4)	4/33 (12.1)	0/33	29/33 (87.9)
Lymph nodes	14/29 (48.3)	11/29 (37.9)	3/29 (10.3)	1/29 (3.5)	25/29 (86.2)
Overall	19/36 (52.8)	14/36 (38.9)	2/36 (5.5)	1/36 (2.8)	33/36 (91.7)

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Table 3: Acute toxic effects (N = 36)

	Grade (% of patients)				
	1	2	3	4	Grade 3/4 (%)
Hematologic					
Anemia	12(33.3)	6(16.7)	2(5.5)	1(2.8)	8.3
Leucopenia	6(16.7)	8(22.2)	2(5.5)	1(2.8)	8.3
Neutropenia	7(19.4)	6(16.7)	1(2.8)	1(2.8)	5.5
Thrombocytopenia	12(33.3)	2(5.5)	1(2.8)		
Febrile neutropenia			1(2.8)		2.8
Nonhematologic					
Nausea	11(30.5)	12(33.3)	5(13.9)	1(2.8)	16.7
Vomiting	9(25)	10(27.8)	3(8.3)		
Mucositis	2(5.5)	10(27.8)	16(44.4)	8(22.2)	66.6
Dermatitis	3(8.3)	12(33.3)	7(19.4)	2(5.5)	25
Dianhoea	4(11.1)	3(8.3)			
Hand-foot synd.	12(33.3)	4(11.1)			

Figures

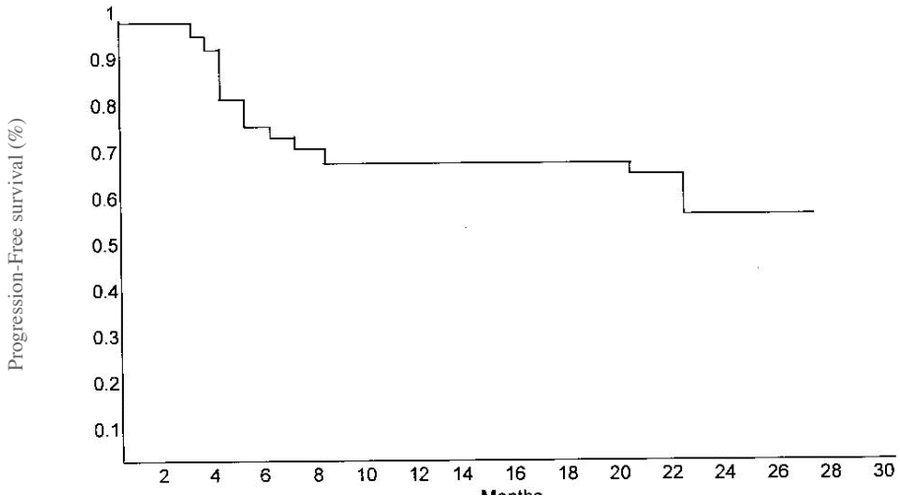

Fig 1. Progression - Free survival for all patients

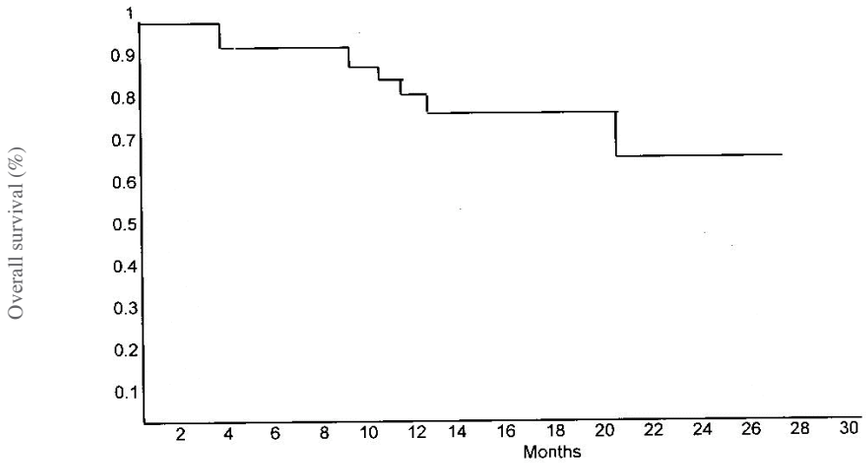

Fig 2. Overall survival for all patients