ORIGINAL ARTICLE ◄

Weekly Cisplatin and Docetaxel plus Concomitant Boost Concurrently with Radiation Therapy in the Treatment of Locally Advanced Head And Neck Cancer: Phase II Trial

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Abstract

Purpose: The aim of this phase II clinical study is to investigate the feasibility of combining concomitant boost radiation therapy regimen (CBRT) with weekly cisplatin and docetaxel and to assess, toxicity and survival in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

Patients and Methods: Between January 2007 to January 2009, 36 patients diagnosed with locally advanced, non-metastatic (stage III–IV) Head and neck squamous cell carcinoma (HNSCC) at Tanta and Menofia University Hospitals were recruited. Radiotherapy dose was 72 Gy in 42 fractions over 6 weeks delivered for gross disease, and uninvolved nodes received 54 Gy in 6 weeks. Chemotherapy consisted of Cisplatin 20 mg/m^2 IV and docetaxel 15mg /m^2 I.V given concurrently with radiotherapy during working week-day time. Both drugs administered weekly (week 1 through 4).

Results: Thirty-six patients were enrolled for response, survival and toxicity. Primary sites were: larynx 19, hypopharynx 9, and oropharynx 8. All patients had T3/T4 disease (58.3% & 41.7% respectively), and only 22.2% of patients had N0 disease. Overall response was observed in 32 patients (88.9%) with 95% confidence interval equal 74.7 to 95.6. Four patients (11.1%) developed progressive disease (95% CI equal 4.58 to 25.67). The 2-year overall survival and progression-free survival rates were, 68.9% (95% CI, 52.6 to 81.6 %) and 53.9% (95% CI, 38.04 to 69.01%), respectively. The 2-year loco-regional control rate was 62.4% (95% CI, 46.0 to 76.2 %). Incidence of grade III was mucositis in 77.8%, acute skin toxicity in 22.2% and neutropenia in only 11.1%

Conclusions: Concomitant boost radiation therapy plus concurrent weekly cisplatin and docetaxel is a feasible schedule in patients with locally advanced head and neck carcinoma, with acceptable toxicity. The survival data in this study was comparable with other trials using CBRT plus concurrent single agent cisplatin either weekly or every three weeks. A randomized phase III study is needed to compare this regimen with bolus cisplatin either weekly or every three weeks.

Introduction

Head and neck cancer accounts for about 3% to 5% of all cancers in the United States. In 2009, an estimated 48,010 people (35,160 men and 12,850 women) developed head and neck cancer, and an estimated 11,260 deaths (8,140 men and 3,120 women) occurred [(1)]. The majority of patients with head and neck squamous cell carcinoma (HNSCC) present with locoregionally advanced disease, which is associated with a poor prognosis despite adequate surgical resection, radiation therapy, or both[(2)]. Recently, four important strategies have emerged for the improvement of therapeutic outcome in the curative treatment of HNSCC: this included the development of altered fractionation radiotherapy[(3)], integration of chemotherapy with radiotherapy[(4)], incorporation of intensity-modulated radiotherapy and the introduction of targeted biological therapy[(5)]. In an effort to improve outcomes, a number of concurrent chemoradiotherapy schedules have been investigated. Several randomized phase III trials have reported a survival and/or organ preservation benefit from the addition of chemotherapy to radiation as primary therapy for locally advanced SCCHN[(6-8)]. A recently updated meta-analysis of trials of chemotherapy in head and neck cancer concluded that the addition of chemotherapy to radiotherapy results in a 4.4% absolute improvement in overall survival compared with radiotherapy alone at 5 years[(9)]. Concurrent chemotherapy was associated with an absolute survival benefit of 6.5% at 5 years[(9)]. Multiple chemotherapeutic agents have been investigated in combination with radiatiotherapy, the most commonly used is the cisplatin[(9)]. Taxanes are potent radiosensitizers, it bind tightly to the β-subunit of microtubules and stabilize them. Tumor cells treated with these drugs are blocked in the G2/M phase of the cell cycle. This phase is more radiosensitive than other parts of the cell cycle. Docetaxel based chemo-radiotherapy was examined in two Japanese dose-escalation studies, used a docetaxel dose of 10–15 mg/m^2 weekly[(10, 11)]. Although several recent studies have investigated a variety of single agents, combinations, and schedules, the optimum regimen is yet to be defined. In our trial, we chose to evaluate the effect and tolerance of the combination cisplatin and docetaxel with radiotherapy in patients with locally advanced HNSCC in a trial to improve our treatment results.

Materials and Methods

This is a prospective phase II multi-centre study included 36 patients diagnosed with locally advanced, non-metastatic (stage III–IV) HNSCC at Tanta and Menofia University Hospitals during the period from January 2007 to January 2009. Patients diagnosed with previous head and neck malignancy, synchronous primary lesions, or had skin cancer within the preceding five years were excluded

from the study. Tumors were staged according to American Joint Committee on Cancer Staging [12]. Tumor stage determined by physical examination, endoscopy, examination under anesthesia, computer tomography (CT), magnetic resonance imaging (MRI), (or both), pelvi-abdominal ultrasound and chest radiograph. Patients underwent through dental/oral examination prior to treatment. Radiotherapy started 10 days after teeth extraction. If the nutritional status of the patient was compromised or patient had GIII dyspahgia, a percutanoeus endoscopic gastrostomy (PEG) tube or nasogastric feeding tube were placed for nutritional support.

Radiotherapy

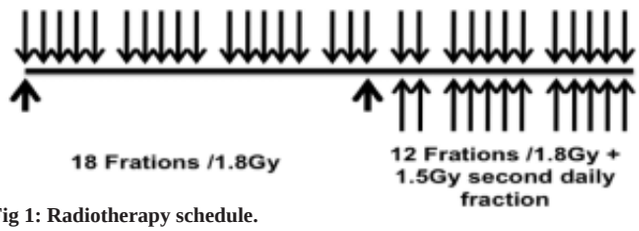

Fig 1: Radiotherapy schedule.

Patients were treated on cobalt ^{60} or 6MV linear accelerator, using a standard three-field technique, consisting of two lateral opposed fields and a single anterior field. Radiotherapy (figure 1) was delivered in 1.8 Gy per fraction, five fractions a week to 54Gy in 30 fractions over 6 weeks to the initial target volume encompassing gross tumor and clinically/radiologically involved nodes along with regions of potential contiguous and lymphatic spread. At 32.4 Gy/18 fractions (i.e., latter part of week 4), a second daily dose of 1.5 Gy/fraction (with at least a 6-h interval) was given to the boost volume covering gross tumor and involved nodes for a total of 18 Gy in 12 treatment days. The primary tumor and clinically/radiologically involved nodes received 72 Gy in 42 fractions over 6 weeks, and uninvolved nodes received 54 Gy in 6 weeks. Clinically/radiologically negative posterior and lower neck nodes received a minimum dose of 50.4 Gy at 3 cm.

Chemotherapy

Cisplatin 20 mg/m^2 IV and docetaxel 15mg /m^2 I.V was given concurrently with radiotherapy during working week-day time. Both drugs administered weekly (week 1 through 4) avoided at start of the concomitant boost.

Follow-Up and Data Analysis

Patients underwent weekly clinical examination during the course of treatment, six weeks after completion of therapy to make sure all acute reaction were subsided completely. Subsequently, patients were assessed every 3 months for the first years, every 4 months in second year. Local tumor control was reported according to CT or MRI requested at least 8 weeks after the end of treatment. All acute and late reaction were recorded according to the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) criteria[13]. Response rate was determined by the WHO Standardized Response Criteria [14].

Statistical methods

The SPSS 10 statistics program was used for statistical analysis. Locoregional control and progression free survival was estimated at 2 years. The primary end points of the study were the treatment response and estimate the 2-year loco-regional control (LRC) rate. Secondary end points were to estimate: the 2-year progression-free survival (PFS), overall survival (OAS), acute and late toxicities. OAS and PFS were measured from the date of start of treatment to death, last follow-up or evidence of disease progression respectively.

Results

Between January 2007 to January 2009, 36 patients with pathologically proven advanced head and neck squamous cell carcinoma were included in our study. Pretreatment patient's characteristics are shown in Table 1. The age of the patients ranged between 28 and 68 year [mean=51.3 (±12.95)]. Male to female ratio 2.6:1. Sixty one percent of the patient had performance status between 0 and 1 according to ECOG performance status scoring system. Twenty patients (55.6%) had stage III disease and 16 patients (44.4%) had stage IV disease. Most of the patients had laryngeal or hypopharyngeal cancers, 52.8% and 25% respectively. The T and N stage distribution using the AJCC staging classification, 6th edition, 2002, is shown in Table 2.

Complete response was recorded in 23 patients (63.9%) and 9 patients (25%) had partial response. The overall response rate was 88.9% (95 % confidence interval [CI] = 74.7 - 95.6) as shown in table 3. Four patients (11.1%) had disease progression (2 patients had primary tumor progression, one patient had nodal progression, and one had disease progression at both sites. The estimated 2-year overall survival, progression-free survival were, 68.9% (95% CI= 52.6 - 81.6 %) and 53.9% (95% CI= 38.04 - 69.01%) respectively as shown in (figure 2 and 3). The 2-year loco-regional control rate was 62.4% (95% CI = 46.0 - 76.2 %) (figure 4).

Both systemic and acute radiation toxicities were reported (table 4). Grade 2 and 3 mucositis were recorded in 22.2 % and 77.8 % respectively no grade IV mucositis. Grade II/III dermatitis were seen in 66.6% of patients (44.4% and 22.2% respectively). Weight loss grade II and III was seen in 33.3% and 8.3% of patients respectively. Acute hematologic toxicity in the form of anemia, and thrombocytopenia was mild and acceptable. The incidence of grade 3 neutropenia was 11.1% and no febrile neutropenia was reported. Blood transfusion and growth factor support due to acute hematologic toxicity were used in 22.3% and 37.9% of patients respectively. Treatment was interrupted for 5 patients (13.9%) they needed hospitalization for supportive treatment.

Discussion

Concurrent chemoradiotherapy has a central role in the management of locally advanced HNC as its survival benefit in comparison to radiotherapy alone is now widely accepted[9, 15]. Altered fractionation schedules represent an important advance in the delivery of radiotherapy in head and neck cancer. Our study is one of several trials merging radiotherapy with chemotherapy. This area of research is still progressing and there remains a need for great caution in combining both modalities as they definitely enhance acute toxicity[16].

The RTOG 90-03 showed clearly that the five year results of hyperfractionation and accelerated fractionation with concomitant boost was superior to standard fractionation for locally advanced head and neck cancer, however this was on the expenses of increased acute toxicity in altered fractionation schedules and there was a slightly higher incidence of late effects with the concomitant boost schedule[17]. As altered fractionation schedules are better than standard fractionation and concurrent chemoradiotherapy is better that radiotherapy alone, many trials tried to combine both methods together. Whether the addition

of altered fractionation to concurrent chemoradiotherapy will result in significant improvement in treatment outcomes without adding undue toxicity remains an unanswered question.

One of the largest study to date using a CBRT plus concurrent chemotherapy was reported by Staar et al[18]. This phase III study including 240 patients compared CBRT alone (69.9 Gy/38 days via 1.8 Gy/d × 3 weeks, then bid XRT with1.8/1.5 Gy weeks 4–5) plus concurrent 5-fluorouracil/carboplatin during weeks 1 and 5. They reported that treatment was tolerable in both arms, with a higher mucosal toxicity after CBRT. Overall response rates (CR + PR) were 92.4% and 87.9% for RCT and RT alone respectively (p = 0.29). This results were in a accordance with a phase II study [19] but included smaller number of patients (52 patients) used CBRT with concurrent weekly cisplatin and docetaxel. They reported an overall response rate of 100% (53% CR and 47% PR). The 2-year locoregional control, progression-free and overall survival rates were 71%, 61% and 65% respectively, which is very close to our results except that our overall response rate was 88.9%. Still acute toxicity was very similar to ours, grade 3 mucositis and dermatitis occurred in 81% and 44% of patients. They reported feeding tube dependence in 17% of patients, although we didn't face this complication but may be because of our shorter follow-up period. Eisbruch et al suggested that this may be attributed to the involvement of pharyngeal constrictor muscles[20].

The use of 1.8Gy per fraction in the above mentioned study and in our study have less toxicity to late reacting tissue as their alpha/beta ration is low ($3Gy_3$), compared to our head and neck tumors which usually have high alpha beta ratio (between 10 and 15 Gy_{10})meaning that the effect on the tumor will be the same and the effect on normal tissues will be less.

In the RTOG Phase II Trial 99-14 [21], 76 patients treated with CBRT and concurrent cisplatin (100 mg/m^2 on days 1 and 22). They reported complete remission in 63 patients (82.9%), PR in 5 patients (6.6%) and 8 patients (10.5%) developed disease progression. They used cisplatin 100mg/m^2 every three weeks. Three patients (4%) died of complications, 19 patients (25%) had acute grade 4 toxicity, and 49 patients (64%) had acute grade 3 toxicity. The estimated 2-year overall survival and disease-free survival rates were 71.6% and 53.5%, respectively this was very close to our patients 2-year OAS and DFS which was 68.9 % and 53.9% respectively. Kumar et al[22] treated 95 patients with CBRT and concurrent weekly cisplatin (35mg/m2). They recorded CR in 59% of patients, and 3-year loco-regional control and overall survival rates were 25% and 27% respectively. Acute grade III/IV mucosal toxicity was seen in 79%. Nasogastric tube placements were required in 26% (25/95) for an average duration of 19.3 days. Other study using taxanes[23] was a pilot study treated 23 patients with stage IV locally advanced squamous cell carcinoma of the head and neck with CBRT plus concurrent weekly paclitaxel. They reported 3- and 4-year actuarial survival rate of 37% and the 3- and 4-year LRC rate of 50%. Most patients (82.6%) had reversible grade 3 acute mucositis. Two patients (9%) developed severe esophageal strictures requiring permanent gastrostomy/tracheostomy, and 2 patients developed other late grade 3+ toxicities. Docetaxel was used in phase I trial at MD Anderson together with concomitant boost RT our regimen is similar to arm 1. Results published in abstract form[24] chemoradiation with weekly docetaxel and cisplatin before initiation of accelerated fractionation (concomitant boost) was feasible and active. Most of the adverse events observed in our study were predictable and manageable. The RTOG acute grade 2 and III mucositis were recorded in 22.2 % and 77.8 % respectively while non of our patients developed grade IV mucositis. Acute skin reactions grade II and III were seen in 66.6% of patients (44.4% and 22.2% respectively). Weight loss grade II and III was seen in 33.3% and 8.3% of patients. 11.1% of our patients had grade 3 neutropenia but no febrile neutropenia was reported. This results is very similar to others results[19, 22, 25,26].

Conclusion

Concomitant boost radiation therapy plus concurrent weekly cisplatin and docetaxel is a feasible regimen in patients with locally advanced head and neck carcinoma, with acceptable toxicity. The survival data in this study was comparable with other trials using CBRT plus concurrent single agent cisplatin either weekly or every three weeks. A randomized phase III study is needed to compare this regimen with bolus cisplatin either weekly or every three weeks.

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Tables

Table 1: Pretreatment characteristics of patients and tumors among 36 patients with locally advanced head and neck cancer.

Characteristic	No.	%
Age	36	
Range 28-68		
Mean 51.3		
Std. Deviation +12.95		
Sex		
Male	26	72.2
Female	10	27.8
Performance status		
0-1	22	61.1
2	14	38.9
Tumor Site		
Larynx	19	52.8
Nasopharynx	8	22.2
Hypopharynx	9	25
T-stage		
T3	21	58.3
T4	15	41.7
N-stage		
N0	8	22.2
N1	16	44.4
N2	12	33.3
Stage Grouping		
Stage III	20	55.6
Stage IV	16	44.4

Table 2: Treatment related acute toxicities.

	Grade I		Grade II		Grade III		Grade V	
	No.	%	No.	%	No.	%	No.	%
Mucositis	0	0	8	22.2	28	77.8	0	0
Early skin reactions	12	33.3	16	44.4	8	22.2	0	0
Nausea and vomiting	20	55.6	6	16.7	0	0	0	0
Weight loss	14	38.9	12	33.3	3	8.3	0	0
Neurotoxicity	12	33.3	2	5.6	0	0	0	0
Hematological toxicities								
Anemia	28	77.8	6	16.7	2	5.6	0	0
Neutropenia	22	61.1	10	27.8	4	11.1	0	0
Thrombocytopenia	10	27.8	0	0	0	0	0	0

Table 5: Late radiation related toxicities.

	No.	%
Subcutaneous edema	26	72.2
Subcutaneous fibrosis	12	33.3
Trismus	4	11.1
Xerostomia	28	77.8

Figures

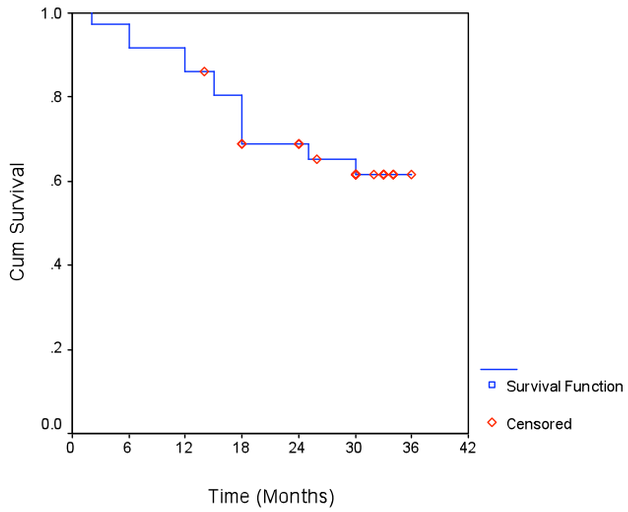

Fig 2: Overall survival of 36 patients with locally advanced head and neck cancer (68.9%, 95% CI = 52.6 to 81.6)

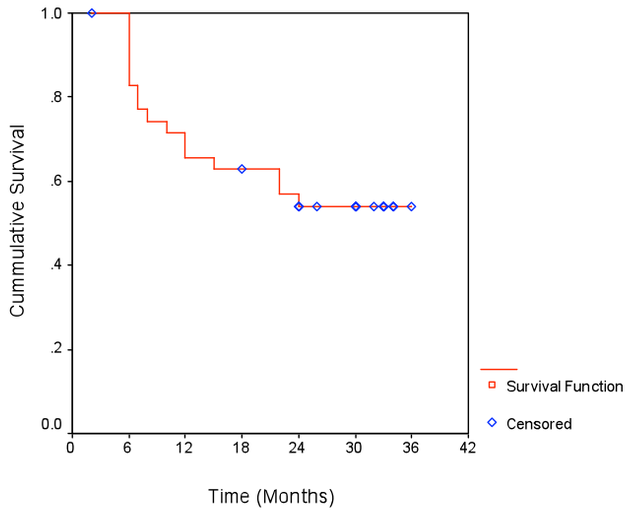

Fig 4: progression free survival of 36 patients with locally advanced head and neck cancer (53.9%, 95% CI = 38.04 to 69.01)

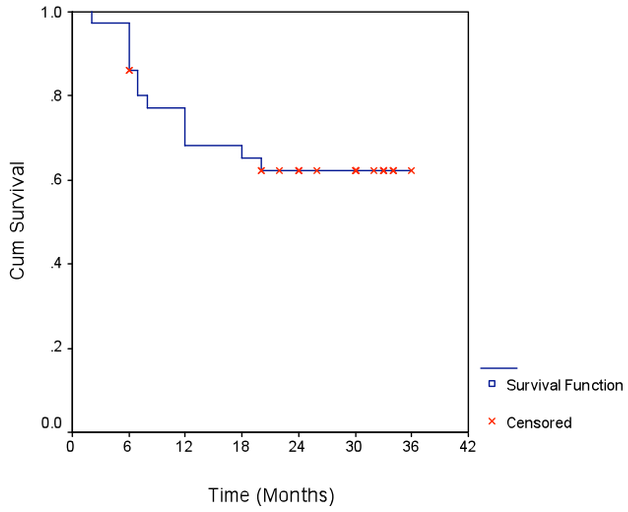

Fig 3: Loco regional control rate of 36 patients with locally advanced head and neck cancer (62.4%, 95% CI = 46.0 to 76.2)