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Low Dose Weekly Paclitaxel Versus Low Dose Weekly Cisplatin with Concomitant Radiation in Locally Advanced Head and Neck Cancers

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Abstract

Purpose: The purpose of this prospective phase III study was to compare the role of concomitant chemoradiation using paclitaxel versus cisplatin in locally advanced head and neck cancers.

Patients and methods: 52 patients were randomly assigned to one of the two concomitant chemoradiation arms: arm I (n=26) and arm II (n= 26) who received injection of paclitaxel 20 mg/m^2 I/V 1 hour infusion before radiation, repeated weekly for 6 cycles, and cisplatin 30 mg/m^2 I/V 1 hour infusion before radiation, repeated weekly for 6 cycles, respectively. The planned radiotherapy dose was 66-70 Gy, 1.8-2 Gy/day, 5#/Week in 6-7 weeks.

Results: Response rates were 76 and 69.2% in arm I and arm II, respectively (P = 0.53). The hematological toxicity was generally mild. On the contrary, non-hematologic toxicities were severe. Grade III mucositis occurred in 32% in arm I and in 23.1% in arm II (P = 0.04). Moreover, grade III dermatitis were encountered in 28% in arm I and 11.5% in arm II (P = 0.03). The 2-year local-regional control figures were 60 and 57.1% in arm I and arm II, respectively(P=0.52) ; however the 2-year progression-free survival figures were 36.8 and 33.3% in arm I and arm II, respectively(P=0.43), while the 2-year overall survival figures were 56 and 50% in arm I and arm II, respectively (P = 0.68).

Conclusion: Both concomitant chemoradiotherapy regimens were easily given in the outpatient clinic. The regimen based on paclitaxel was more effective; however, the difference was insignificant.

Keywords: Concomitant chemoradiotherapy; Cisplatin; Paclitaxel; Head and neck cancer

Introduction

Head and neck cancer constitutes a heterogeneous group of malignancies which exceeds half a million cases annually, ranking it as the fifth most common cancer worldwide. Head and neck cancer accounts for about 3% to 5% of all cancers in the United States [1]. It represents 17% of all malignant tumours in Egypt [2].

The treatment of patients with unresectable, locally advanced head and neck squamous cell carcinoma (HNSCC) remains a challenge. Radiation has been the standard treatment for locally advanced, unresectable HNSCC.Even the most effective radiotherapy regimens result in local control rates not exceeding 50-70% and disease-free survival rates not more than 30-40%. This circumstance has stimulated the investigation of treatments combining radiotherapy and chemotherapy ; the most promising approach being the administration of chemotherapy concurrent with radiation [3]. A number of randomized studies have shown improved results when radiation was combined with concurrent cytotoxic agents compared with radiation alone despite increased toxicity of the combined arm, notably hematological and mucosal toxicities, which limited the ability to deliver full doses of radiation or the chemotherapeutic agents [4-8]. Although most trails of concurrent chemoradiation have used cisplatin in combination with 5-fluorouracil (5-FU), there is at present no evidence that this combination performs better than cisplatin alone [9]; thus, the optimal drugs, doses and schedules of concurrent chemotherapy and radiotherapy for head and neck cancer are not known.

We used cisplatin arm as a control arm because cisplatin is one of the most extensively used agents effective in the management of squamous cell carcinoma of head and neck which can be used either as a single agent or combined with a variety of other drugs and has shown improved overall response rate up to [10].

Paclitaxel is a newer active single agent in head and neck cancer,it was used in the trial arm in low dose weekly schedule. Observation suggests that paclitaxel induces microtubule stabilization, and a cell cycle blockade at the G2 phase to mitosis (G2/M) transition, the most radiosensitive portion of the cell cycle [11,12]. An additional mechanism seems to involve enhanced tissue oxygenation. Recently it was shown that paclitaxel activates c-Jun-terminal-kinase (JNK) or protein-kinase A (PKA), leading to the phosphorylation of the antiapoptotic Bcl-2 protein. Phosphorylation of Bcl-2 decreases its binding to the proapoptotic Bax protein and an increase in the free Bax level promotes apoptosis [13]. This apoptotic effect of paclitaxel is independent of the p53 pathway [14].

Keeping this in mind in our setting we planned to compare the role of concomitant chemoradiation using paclitaxel versus cisplatin in locally advanced head and neck cancers.

Patients and Methods

Between January 2009 and June 2010, 52 patients with locally advanced squamous cell carcinoma of head and neck who attended to Clinical Oncology and Nuclear Medicine Department, Mansoura

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University Hospital, were randomly assigned in this prospective phase III study.

Eligibility criteria

Patients with biopsy proven HNSCC stages III and IV tumors for all sites were eligible. Patients must have been either ineligible for curative resection or have refused surgery and must have had no prior radiotherapy to the head and neck region or chemotherapy. Patients with obvious metastatic disease on diagnostic imaging were excluded from the study. Additional eligibility criteria included the following: eastern co-operative oncology group (ECOG) performance status ≤ 2, age greater than 18 years, absolute granulocyte count greater than 2000/mm^3, platelet count greater than 100,000/mm^3 , serum bilirubin, SGOT, SGPT, serum creatinine within normal limit, no other history of active malignancy and no other serious medical disease.

Pretreatment evaluation

Pretreatment evaluation included complete history, physical examination, head and neck examination including mirror and panendoscopic examination, histopathologic examination of the primary tumor or cervical lymph nodes, complete blood count, blood chemistry including liver function tests, and kidney function, computed tomography and or magnetic resonance imaging of the head and neck to define the extent of the disease and metastatic workup including chest x-ray and imaging of liver by ultrasound or computed tomography in all patients. Bone scan was not routinely performed and was restricted to those with bone pain or elevated serum alkaline phosphatase. Dental care was applied to each eligible patients before therapy.

Treatment schedule

All patients were treated on a linear accelerator or cobalt - 60 teletherapy unit. Patients of both arms received a total dose of 66-70 Gy radiation, 200 cGy/day, 5#/Week in 6-7 weeks. Arm I patients received concurrent dose of paclitaxel 20 mg/m^2 I/V 1 hour infusion with premeditation 4-6 hours before radiation, repeated weekly for 6 cycles. Arm II patients received concurrent dose of cisplatin 30 mg/m^2 I/V 1 hour infusion with full hydration 4-6 hours before radiation, repeated weekly for 6 cycles.

During the study, patients were hospitalized and given symptomatic treatment as needed. Patients were reviewed every week and assessed with complete clinical examination including indirect laryngoscopy and in addition, were evaluated for toxicities according to RTOG acute radiation morbidity scoring criteria. Systemic toxicities were graded according to the common toxicity criteria, version 2. Laboratory and clinical toxicities were considered acute if discovered during the first 12 weeks after the initiation of therapy.

Post-treatment evaluation

Response was assessed six weeks after completion of radiotherapy by clinical examination, endoscopic examination, and CT and/or MRI of head and neck. Criteria for response were as follows: complete response (CR) was defined as complete regression of all evidence of tumor. Partial response (PR) was defined as an estimated decrease in tumor size of 50% or more. Stationary disease (SD) was defined as <50% decrease in tumor size or <25% increase in pretreatment tumor size. Progressive disease (PD) was defined as > 25% increase in pretreatment tumor size.

Re-evaluation was done at 3 months interval during the first two years of follow-up unless any manifestations of progression were developed. Chest radiography and ultrasonography of the liver were performed every 6 months.

End points

The primary endpoints were to analyse and compare locoregional control and acute adverse effects in both treatment arms. The secondary endpoints were to analyse and compare progression-free survival and overall survival in both treatment arms.

Statistical methods

All data were categorical and represented as number and percent. The baseline characteristics and adverse effects of the two treatment arms were compared using the Chi-square test. Confidence intervals (CIs) were calculated using Cox's proportional hazard model. Overall survival, local-regional free survival and progression-free survival were calculated using the Kaplan-Meier method. Mann-Whitney U test used to compare the median responses, overall survival, local-regional free survival and progression-free survival in both treatment groups.

Prognostic factors related to response, overall survival, local-regional free survival and progression- free survival were assessed using Cox proportional hazards regression model.

Informed consent was obtained from all patients, and ethical committee approval was received by our participating center.

The randomization scheme was a permuted block design with an equal probability of assignment to either treatment arms. Patients were stratified by primary site of disease and stage of disease and were then randomized to receive one of the two treatments planned in the trial.

Results

Patient's characteristics

From January 2009 to June 2010, 52 patients were recruited and randomly assigned into two treatment arms, either arm I with 26 patients or arm II with 26 patients. . Data of one case was deleted list wise in arm I because he could not be subsequently contacted. A total of 51 patients received complete treatment as defined per protocol or with an acceptable variation with respect to overall days of therapy and total dose.

Table 1 shows the pre-treatment patients characteristics. They were well balanced among the both treatment groups. The median age was 58 years, ranging from 20 to 70 years. Males were predominant representing 76.5%, 60.8% of our patients were smokers. The nasopharynx was the most common primary site representing 39.2%. All patients were stage III (41.2%) and stage IV (58.8%).

Response

Response assessment was done 6 weeks after the completion of treatment. The overall response rates were 76% (95% CI, 0.564 – 0.884) and 69.2% (95% CI, 0.498 – 0.835) respectively for arm I and arm II, with no statistically significant difference (p=0.58). Complete response were achieved in 60% of patients in arm I versus 53.8% for arm II but the difference was statistically insignificant (P=0.66). Partial response was achieved in 16% versus 15.4% in arm I, II respectively (p=0.95) (Table 2).

Character	Total		Arm I		Arm II		P Value
	No.	%	No.	%	No.	%	
Age (years):							
<60	31	60.8	15	60	16	61.5	0.9104
≥60	20	39.2	10	40	10	38.5	
Sex:							
Male	39	76.5	20	80	19	73.1	0.56.01
Female	12	23.5	5	20	7	26.1	
Smoking:							
Smoker	31	60.8	15	60	16	61.5	0.9104
Non smoker	20	39.2	10	40	10	38.5	
ECOG score							
1	31	60.8	15	60	16	61.5	0.9104
2	20	39.2	10	40	10	38.5	
Site:							
Oral cavity	5	9.8	2	8	3	11.5	0.6709
Nasopharynx	20	39.2	12	48	8	30.8	0.2076
Oropharynx	6	11.8	2	8	4	15.4	0.4132
Hypopharynx	10	19.6	4	16	6	23.1	0.5245
Larynx	10	19.6	5	20	5	19.2	0.9448
Grade							
I	11	21.6	5	20	6	23.1	0.7894
II	10	19.6	6	24	4	15.4	0.4385
III	12	23.5	5	20	7	26.9	0.5601
Undifferentiated	18	35.3	9	36	9	34.6	0.9176
T-stage							
T2	10	19.6	4	16	6	23.1	0.5245
T3	31	60.8	16	64	15	57.7	0.9104
T4	10	19.6	5	20	5	19.2	0.9448
N-stage:							
N0	11	21.6	5	20	6	23.1	0.7894
N1	11	21.6	4	16	7	26.9	0.3430
N2	20	39.2	13	52	7	26.9	0.0667
N3	9	17.6	3	12	6	23.1	0.2995
AJC stage:							
III	21	41.2	11	44	10	38.5	
IV	30	58.8	14	56	16	61.5	0.6878

Table 1: Patient Characteristics.

Response	Arm I		Arm II		P Value
	No.	%	No.	%	
Complete response	15	60	14	53.8	0.6573
Partial response	4	16	4	15.4	0.9518
Stationary disease	3	12	4	15.4	0.7254
Progressive disease	3	12	4	15.4	0.7254
Overall response	19	76	18	69.2	0.5881

Table 2: Response.

Toxicity and treatment compliance

As regard toxicity, toxicity was higher in the paclitaxel group but it was tolerable and manageable. Table 3 show the site and grade of acute effects by treatment groups. The most common sites of grade 3 or worse acute side effects were the skin and the mucous membranes. Compared to arm II, arm I had significantly increased grade 3 or worse acute side effects as dermatitis (P=0.03), mucositis (P=0.04).

Survival

The median local recurrence free survival was 17 months (ranging from 6-26 months) in arm I versus 15 months (ranging from 3-26 months) in the arm II. Locoregional control rate at two years was (60%) in arm I compared with (57.1%) in arm II but the difference was statistically insignificant (P=0.52). Results of Kaplan- Meier estimates of local-regional control in both treatment groups are shown in Figure 1.

Progression includes the following events: local, regional, loco-regional and distant failure. The median progression-free survival was 11 months (ranging from 3-26 months) in arm I vs 9 months (ranging from 2-26 months) in arm II (P=0.43). In addition, 2-year progression-free survival in arm I 36.8 % vs 33.3% in arm II, with statistically insignificant difference (P=0. 28), (Figure 2).

At a median follow-up of 20 months of all analyzed patients, the median overall survival in arm I was 19 months(ranging from 7-26 months) vs 17 months(ranging from 5-26 months) in arm II, with no statistically significant difference (P=0.16). The 2-year overall survival in arm I was 56% vs 50% in arm II, with no statistically significant difference (P=0. 68), (Figure 3).

Pattern of treatment failure

The primary site was the most common location of treatment

failure. The 2-year locoregional failure rates were 40% in arm I vs 42.9% in arm II, (P=0. 19). However, the incidence of distance metastases at 2-years was 4% in arm I vs 7.7% in arm II (P=0.43).

Prognostic factors

On multivariate analysis for locoregional control, T category (T4 vs T2, T3; P=0.03), tumor site (oral cavity or oropharynx vs all other sites; P=0.04), and N–category (N2-N3 vs N0, N1; P=0.05),) were significant independent adverse prognostic factors for locoregional control. However, on multivariate analysis for progression- free survival, T category (T4 vs T2, T3; P=0.01), sex (male vs female; P=0.024) and smoker patients (P=0.03) had independent adverse prognostic impact on progression-free survival. In addition, on multivariate analysis for survival, sex (P=0.03), poor performance status (P=0.03), T4 (P=0.01), N2-N3 category (P=0.04) and stage IV (P=0.01) were independent factors associated with poor prognosis for survival.

Organ/Tissue	Grade	Arm I		Arm II		P Value
		No.	%	No.	%	
Anemia	1 2	8 8	32 32	9 8	34.6 30.8	0.8658
Leucopenia	1 2	8 7	32 28	7 8	26.7 30.8	0.7150
Thrombocytopenia	1 2	4 6	16 24	5 5	19.2 19.2	0.8086
Skin toxicity (dermatitis)	1 2 3	9 9 7	36 36 28	19 4 3	73.1 15.4 11.5	0.03007
Mucous membrane (mucositis)	1 2 3	1 16 8	4 64 32	10 10 6	38.4 38.4 23.1	0.04845
Salivary gland (xerostomia)	1 2	7 16	24 64	6 16	23.1 61.5	0.8150
Plarynx/Eosphagus (dysphagia)	1 2 3	8 10 7	32 40 28	7 10 6	26.7 38.5 23.1	0.9942
Subcutaneous tissue (neck edema)	1 2	10 4	40 16	9 1	34.6 3.8	0.2693
Taste sensation (dysgeusia)	1 2	22 3	88 12	18 3	69.2 11.5	0.8186
Weight loss	1 2	20 4	80 16	19 3	73.1 11.5	0.7750

Table 3: Acute adverse effects in both treatment arms.

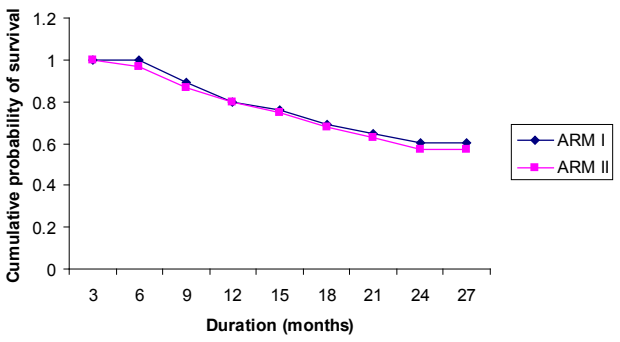

Figure 1: Cumulative probability of local-regional free survival in both treatment arms.

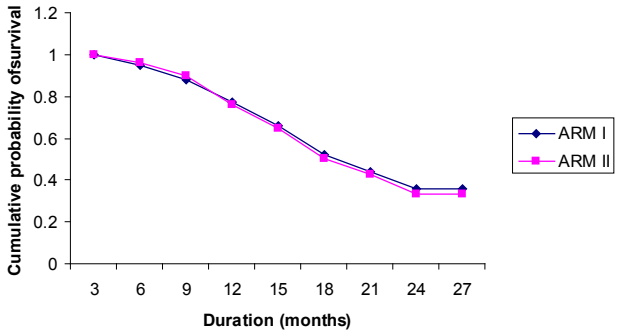

Figure 2: Cumulative probability of progression free survival in both treatment groups.

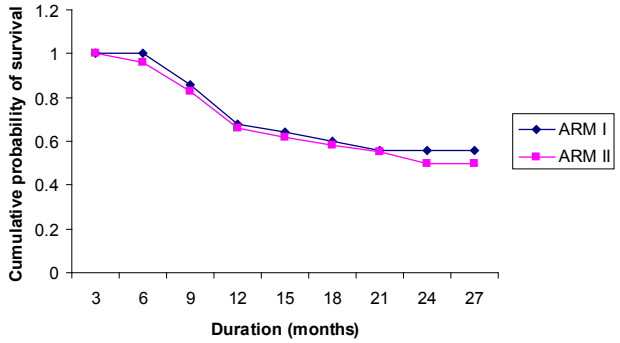

Figure 3: Cumulative probability of overall survival in both treatment arms.

Discussion

Locally advanced head and neck cancer is a great challenge for oncologists. The most aggressive non-surgical treatment is the combination of chemotherapy and radiation [15] however, grade 3 and 4 toxicity also significantly increase along with more intensive schedules [16].

This study was intended to compare concomitant chemoradiation using newer active agent paclitaxel in low dose weekly schedule versus most extensively used agent cisplatin with conventional radiation in locally advanced head and neck cancers.

In our study. No significant difference in efficacy was noted between both arms. This was true for the primary end point, response rates and locoregional control, as well as for other end points, progression-free survival and overall survival. Although some patients in our study in the paclitaxel arm sustained high local toxicity, mucositis and dermatitis, but it was tolerable and manageable**.** No dose limiting systemic toxicity was encountered in our study.

A 60% complete response was achieved with paclitaxel versus 53.8% with cisplatin in patients with highly advanced HNSCC. This response achieved in our study in the paclitaxel arm is comparable to those achieved with the regimens employed by Hoffmann et al. [17] and by Steinberg et al. [18]. RK Jain et al. reported 73% CR paclitaxel versus 64% with cisplatin in patient with HNSCC with the same regimen used in our research [19].

Hoffman et al. [17] studied the combination of conventional

radiotherapy with weekly 1 hour infusion of paclitaxel in 18 patients with unresectable HNSCC. Paclitaxel was given at a starting dose of 20 mg/m^2, and subsequent dose escalations of 10 mg/m^2 were applied. Radiation therapy was administered over 6 to 7 weeks with 200 cGy daily, up to total doses of 60-70 Gy. The maximum tolerated dose of paclitaxel in this setting was 30 mg/m^2 /week, with mucositis being dose limiting.

Steinberg et al. [18] described a study in which 24 patients with stage III and IV HNSCC were administered radiotherapy (daily fractionation to total doses of 66 to 72 Gy) in combination with paclitaxel given as 24-hour continuous infusions on days 1, 22, and 43. Dose escalations of 75, 90 and 105 mg/m^2 were given. This regimen achieved CR of 72% at the primary site. The maximum-tolerated dose was retrospectively determined to be less than 75 mg/m^2, because more than 50% of the patients developed febrile granulocytopenia at that dose. Significant local toxicities also were reported. Most notable of these were skin toxicity and grade 3 mucositis, necessitating enteral feeding tubes.

Lovey et al. [20] examined the use of low-dose paclitaxel concurrently with radiation for patients with locally advanced head and neck cancers. Twenty-six patients were treated with external beam radiotherapy and received concomitantly 2 mg/m^2 paclitaxel three times a week. Beside an acceptable efficacy (RR: 65%, 2-year overall survival 46%) the treatment was well tolerated and resulted in a favorable toxicity profile. This regimen is resource effective and allows successive therapy if necessary, and therefore may serve as an alternative for patients in poor condition with locally advanced head and neck.

Tishler et al. [21] reported a study in which 14 patients with stage III and IV HNSCC were treated with paclitaxel administered at a dose of 100 mg/m^2/3 weeks), in combination with external beam radiation (daily fractionation to total doses of 60 to 70 Gy). Of these 14 patients, 10 had received prior cisplatin, fluorouracil, and leucovorin. Overall, the concurrent therapy achieved a CR in 13 (92%) of the 14 patients. Three of the 13 went on to develop recurrent disease (one with distant metastasis and two with local/regional disease). The major toxicities included grade 3,4 mucositis . Although the CR reported by Tishler et al. [21] was higher, comparisons of efficacy are difficult to interpret because 67% of those patients with a CR had received prior therapy.

Although no conclusions can be drawn as the optimal regimen based on this comparison of our study with the ones above, both concomitant chemoradiotherapy regimens were easily given in the outpatient clinic. The regimen based on paclitaxel was more effective; however, the difference was not enormous. Because of the shorter duration of follow-up and small sample size. Therefore, further studies are needed with large sample sizes and long duration of follow-up.

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