Response Rate and Toxicity of Docetaxel / Cisplatin /5FU in Comparison with Cisplatin / 5FU Induction Chemotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma

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Abstract

Introduction: Response to chemotherapy is a reliable marker for radiation sensitivity in patients with locally advanced head and neck squamous cell carcinoma. We compared the response rate and toxicity after two cycles of chemotherapy using Docetaxel / Cisplatin /5FU or Cisplatin / 5FU among these patients.

Materials and methods: We randomly assigned 16 to 75 years old patients with stage III or IV non-metastatic locally advanced head and neck squamous cell carcinoma to receive either DCF or CF every 3 weeks for two cycles. All patients who received at least one and two cycles of chemotherapy were considered for toxicity and response evaluation respectively.

Results: Seventy patients underwent randomization, 36 and 34 patients were assigned to Docetaxel / Cisplatin /5FU and Cisplatin / 5FU groups respectively. Three and 8 patients were excluded after randomization and before receiving any chemotherapy in Docetaxel / Cisplatin /5FU and Cisplatin / 5FU groups respectively. Finally 30 and 25 in Docetaxel / Cisplatin /5FU group and 25 and 23 patients in Cisplatin / 5FU group were evaluated for toxicity and response respectively. Response rate (complete and partial response) was %83 (35% complete and 48% partial response) and %84(16% complete and 68% partial response) in Cisplatin / 5FU and Docetaxel / Cisplatin /5FU groups respectively (P= 0.28). There was no differences in complete response rate between two groups (P=0.18). Neutropenia, phlebitis and mucositis were more common in Cisplatin / 5FU group without statistically significant difference. Constipation was significantly more common in Cisplatin / 5FU group (P= 0.008). Diarrhea, alopecia and febrile neutropenia were significantly more common in Docetaxel / Cisplatin /5FU group (P= 0.006, 0.01 and 0.03 respectivly).

Conclusion: We could not find any significant differences between response to Docetaxel / Cisplatin /5FU and Cisplatin /5FU combination chemotherapy among Iranian patients with locally advanced head and neck squamous cell carcinoma. However, for better evaluation, larger studies with better designs are being conducted in our center.

Introduction

Squamous-cell carcinoma of the head and neck accounts for 6% of cancers all over the world and ranks sixth among the most common cancers[(1)]. More than 500,000 new cases are diagnosed

worldwide annually and more than sixty percent of them present as an advanced disease with a poor prognosis [2]. In Iran, head and neck SCC accounts for about six percent of all cancers [3], and based on our practice experience, we believe more than two thirds are locally advanced.

Radiotherapy in combination with chemotherapy is the standard treatment for Locally Advanced Head and Neck Squamous Cell Carcinoma (LAHNSCC) to preserve organs [4]. Meta analysis has shown slightly better results for concurrent chemoradiation in comparison with induction chemotherapy followed by radiotherapy. The absolute benefit of concurrent chemoradiation in comparison with induction chemotherapy is just 3% [5]. Treating LAHNSCC with upfront concurrent chemoradiation may increase the rate of tracheostomy due to increased edema in patients with threatened airway and may also require one or two more simulation and treatment planning during the radiotherapy course because of tumor shrinkage, especially in bulky tumors.

Response rates up to 80% have been reported for new chemotherapy combinations in head and neck cancers, especially by adding Docetaxel to the combination [6-9]. Therefore, starting with induction chemotherapy in LAHNSCC can result in response in the majority of these patients and reduce the need for tracheostomy and additional simulation and treatment planning.

It has been also shown that induction chemotherapy could eradicate micro metastases and reduce distant recurrence rate. [10-13]

Nowadays, Docetaxel in combination with Cisplatin and 5Fu is the preferred regimen for induction chemotherapy in LAHNSCC according to several phase III studies [6-8, 14] showing increased survival, progression free survival, organ preservation and response rate when compared with non Docetaxel containing regimens. However, the increased response rate due to adding Docetaxel to the chemotherapy regimen in these trials is not a consistent finding.

In our center, the waiting list for radiotherapy is long and facilities for repeated simulation and re-planning are insufficient so most LAHNSCC cases in our center are treated with 2 or 3 cycles of induction chemotherapy using different chemotherapy regimens. We conducted this study to compare the response rate as the primary objective of two different induction chemotherapy regimens (Docetaxel, Cisplatin and 5Fu (DCF) versus Cisplatin and 5Fu (CF) in our patients with LAHNSCC.

Materials and methods

This study was performed at Imam Hossein Hospital from June 2008 to January 2010. An overall clinical response in the range of 60-80% was anticipated on the basis of similar studies reported in the literature. The sample size was calculated using the Simon method, with a type I error of 5% and a study power of 80%. The target enrollment was estimated to be 43 evaluable patients. Therefore, we considered 70 patients for further assurance assuming the possible loss to follow-up cases.

At first, an oral informed consent was obtained. Then, baseline evaluation was performed including complete disease evaluation, complete medical history taking, Eastern Cooperative Oncology Group (ECOG) performance status, physical examination, pan endoscopy, pregnancy test if applicable, CBC, SGOT, SGPT, total bilirubin, creatinine, CT scan of the head and neck, chest CT scan, abdominal ultrasonography, and bone scan when indicated. Patients with histologically proven head and neck squamous cell carcinoma and undifferentiated carcinoma of the nasopharynx that was non-metastatic at presentation and had a measurable tumor in stage III or IV (T3 or T4 or N2 or N3), based on American Joint Committee on Cancer were enrolled. Inclusion criteria were age between 16 and 75 years of age, performance status of less than 2 in ECOG score and acceptable bone marrow, liver and renal function tests. Any patient with previous chemotherapy or radiotherapy to the head and neck, uncontrolled diabetes mellitus, uncontrolled pulmonary or cardiovascular disease, any grade of preexisting neuropathy was excluded. Lactating and pregnant women were also excluded. After that, patients were stratified based on age and performance status, and randomized to receive either CF or DCF regimens.

Treatment schedule

After randomization, patients received two cycles of chemotherapy and were evaluated for response; then, treatment continued with definitive chemoradiation or surgery followed by adjuvant chemoradiation based on the physician's opinion.

In the CF regimen group, 100 milligram per

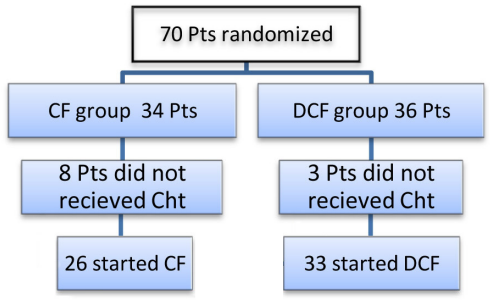
square meter of Body Surface Area (BSA) of cisplatin was administered as a 2-hour infusion intravenously on day one followed by 5flourouracil (1000 milligram per square meter of BSA) as a 24-hour intravenous continuous infusion for 5 consecutive days. Chemotherapy in the DCF group consisted of the same schedule for cisplatin and 5flourouracil as the CF group but at different doses (75 and 750 milligram per square meter of BSA respectively) and docetaxel (75 milligram per square meter of BSA) was added on day 2 after completion of day one as a one-hour intravenous infusion and 5flourouracil was continued for four more days thereafter.

Chemotherapy was repeated every 3 weeks in both groups. No prophylactic growth factor was allowed in this study. If chemotherapy was postponed for more than 6 days because of neutropenia and/or leucopenia, five prophylactic doses of granulocyte colony stimulating factor were prescribed after the next cycle. On the scheduled first day of the second cycle, if neutrophil≥1500 and Plt≥100000, therapy was performed within the scheduled time and dose; if not, a 3-day delay was given. Any grade III or IV hematologic or non hematologic toxicity on the scheduled first day of the second cycle delayed chemotherapy until regression to grade I or less. Treatment was discontinued if it could not be administered after 2 weeks of scheduled time due to any reason. On the first day of each cycle, clinical examination was performed and creatinine, total bilirubin, SGPT, SGOT and CBC were assessed.

All patients who received at least one dose of the study medication were considered as evaluable for toxicity. Maximum grade of toxicity was reported by cycle. Hematologic and non hematological toxicities were recorded every cycle. Toxicity was graded according to the WHO criteria [15]. All patients who received two cycles of chemotherapy were considered evaluable for response. The objective response rate was determined by tumor measurement using the Response Evaluation Criteria in Solid Tumors (RECIST) [16] 21 days after the commencement of the second cycle of chemotherapy, based on CT scan or MRI imaging.

Results

Seventy patients with head and neck squamous cell carcinoma who were referred to our centre and met requirements for participation in this study were randomized to CF and DCF groups. The DCF and CF groups contained 36 and 34 participants, respectively. Three patients in the DCF group and eight patients in the CF group did not start chemotherapy.



We prescribed 60 and 48 cycles of chemotherapy in the DCF and CF groups, respectively. Twenty-five and 23 patients were evaluated for response to treatment in the DCF and CF groups, respectively. Eight patients received just one cycle of chemotherapy (seven patients in the DCF and one patient in the CF group). Four patients did not return after the first cycle of chemotherapy for unknown reasons (three in the DCF and one in the CF group). Two patients died after the first cycle of chemotherapy (one in the DCF group due to an unknown reason and one in the CF group due to neutropenic fever). Two patients died due to pulmonary embolism after the second cycle (one in each group). One patient in the DCF group died due to opium overdose on day one of cycle two. One patient in the DCF group developed disseminated intravascular coagulation on day three of cycle two; this patient was admitted to the intensive care unit and discharged after 10 days. Four patients in the CF and one in the DCF group started the second cycle of chemotherapy with delay due to non treatment related reasons.

Table 1 demonstrates the difference between the two groups treated with DCF and CF based on sex, age, cancer site and staging. As this table shows, there was no significant difference between the two chemotherapy groups in listed variables.

Response rate was equal between the two groups (83 and 84 percent in CF and DCF groups respectively). Although the complete response rate was almost more than twice in the CF group (35%) in comparison with the DCF group (16%), but the difference was not statistically significant (Table 2).

Treatment related delay in starting the second cycle was more common in the CF group in comparison with the DCF group (45.8% vs. 10%, P=0.0001) and the most common reason for the delay in the administration of the second cycle was neutropenia (73% and 70% of delays for CF and DCF respectively).

Comparison of the chemotherapy adverse events between the two groups showed no significant difference in hematologic toxicity, nausea and vomiting, phlebitis, neuropathy, mucositis and renal and liver function tests. However, neutropenia, phlebitis and mucositis were nonsignificantly more common in the CF group. Febrile neutropenia and grade III and IV diarrhea was more common in DCF group (Table 3).

Discussion

Our study showed an equal response rate for DCF and CF chemotherapy in contrast to some recent phase III trials [6-8, 14]. We achieved a response rate of 83-84 percent in our patients that is higher than hallmark phase III studies conducted in Europe and North America. In TAX 323 [8] and 324 [7], a maximum response rate of 68 and 72 percent were reported respectively that is lower than our study. Moreover, it should be noted that we prescribed only two cycles of chemotherapy in comparison with 3 and 4 cycles in TAX 323 and 324, respectively. There were also considerable differences in clinical complete response between our study and TAX studies. We achieved complete response rates of 16 and 35 percent in the DCF and CF groups respectively although the difference was not statistically significant, the complete response rate in both groups was much higher than pivotal trials that reported a complete response rate of 8.5 versus 6.6 percent for TAX 323 and 17 versus 15 percent for tax 324 in the DCF and CF groups, respectively.

Squamous cell carcinomas of the different sites of the head and neck have different behaviors and prognoses. Most studies including TAXs excluded nasopharyngeal carcinoma but in our study, more than a quarter (23 and 33 percent of patients in CF and DCF groups respectively) had nasopharyngeal

Table1: Demographics of study participants.

	CF (26)	DCF(33)	P value
Male sex No (%)	23(88.4)	28(84.4)	0.68
Age median(range)	52.7(16-75)	54.6(21-75)	0.62
Age No (%) <35 Yrs 35-49 Yrs 50-64 Yrs >65 Yrs <50 Yrs >50 Yrs	 3 (11.5) 3 (11.5) 15 (57.7) 5 (19.2) 6 (23) 20 (77)	 3 (9.1) 7 (21.2) 12 (36.4) 11 (33.3) 10 (30.3) 23 (69.7)	 0.33 0.57
Cancer site Hypopharynx Larynx Oral cavity Oropharynx Nasopharynx	 5(19.2) 13(50) 1(3.8) 1(3.8) 6(23.1)	 3(9.1) 16(48.5) 2(6.1) 1(3) 11(33.3)	 0.77
T stage T2 T3 T4	 3(11.5) 14(54) 9(34.5)	 11(33) 13(39) 9(28)	 0.14
N stage N0 N1 N2 N3	 11(42.5) 3(11.5) 11(42.5) 1(3.5)	 10(30) 5(15) 17(52) 1(3)	 0.72

Table2: The response rate of treatment methods.

	CF (N=23)	DCF (N=25)	P Value
Complete response rate % (N)	35(8)	16 (4)	0.18
Partial response rate % (N)	48 (11)	68 (17)	
Overall response rate (partial + complete) %	83	84	0.28

carcinoma (80% was undifferentiated carcinoma), which usually responds better to chemotherapy as compared to other sites in the head and neck[17]. However, it was interesting that in spite of more cases of nasopharyngeal carcinoma in our DCF group, clinical complete response was more common in the CF group (35 versus 16 percent).

Stage is a predictor of response to chemotherapy. In TAX 323, all patients were unresectable, 70 percent had T4 and 72 percent had N2-3 disease [8]; also, in TAX 324, 43 and 65 percent of the patients had T4 and N2-3 [7], respectively. We achieved higher rate of complete response and also overall response rates in comparison with aforementioned studies that could be explained by the lower percent of patients with T4 and N2-3 disease (30 and 50 percent respectively).

The higher overall and complete response rates in our study could be related to more favorable patient population (more nasopharyngeal undifferentiated carcinoma and lower tumor and nodal stage) although it is not conclusive as we achieved equal overall and higher complete response rates in the CF group when compared to the DCF group that is in contrast with other studies. Ethnic and racial factors may explain the differences between our study and other surveys.

More than half of the patients in major neoadjuvant trials in head and neck cancer have had oropharyngeal cancer. This is in contrast to our study which had less than 5 percent oropharyngeal cancer cases included. Oropharyngeal cancer includes two different categories, HPV positive and HPV negative. HPV is found in about 26 percent of head and neck SCCs [18] and HPV positive oropharyngeal cancers is encountered in more than fifty percent of all oropharyngeal cancers [19-21] with a more favorable prognosis and better response to chemotherapy [22-23].

The number of HPV positive oropharyngeal cancers in a trial may improve results. HPV positivity in head and neck SCCs may differ with race and ethnicity [24]. In a report by Seraj et al, HPV positivity rates of 10 and 16 percent were found for HPV16 and HPV 18 in oral tongue SCCs, respectively[25]. However we do not know the exact rate of HPV positivity in other head and neck SCCs in Iranian patients.

Genetic factors can also affect tumor response to different chemotherapy agents. Nucleotide excision repair pathway is an important pathway in response to DNA damaging chemotherapy such as cisplatin. ERCC1 is an important molecular marker for nucleotide excision repair and cisplatin resistance [26].

Polymorphism in the ERCC1 gene also affects the prognosis of head and neck cancer patients and response to cisplatin based chemotherapy [27]. Chiu et al. [28] evaluated response to cisplatin based chemotherapy in head and neck cancers in Taiwan. Forty six percent of their patients had high expression of ERCC1 with a response rate of 50 percent in comparison with 90 percent in ERCC1 low expression patients. High expression ERCC1 was also more common in non hypopharyngeal and laryngeal SCCs. Jun et al. [29] also evaluated ERCC1 expression in LAHNSCC and the relationship between ERCC1 and response to concurrent cisplatin based chemoradiation. Seventy three percent of the patients had high expression levels of ERCC1 and response rate was 83 versus 52 percent for tumors with low and high expression levels, respectively.

ERCC1 expression is different between ethnic groups. Gao et al. showed racial disparities in Americans of different descent regarding polymorphism in some genes including ERCC1 [30]. Other molecular markers such as different types of Beta tubullin expression may predict response to taxanes and affect the patient's outcome [31-36]. Cullen et al. [37] evaluated several tumor markers in initial biopsies from the TAX 324 trial and showed a relationship between β-tubullin-II expression and Docetaxel benefit.

In our opinion, some of the differences between our results and other pivotal studies may be related to ethnical disparities. We intend to evaluate molecular markers in biopsies of our patients.

Like most other studies [6-8], we noted no statistically significant difference in critical adverse

Table3: Comparison of the chemotherapy adverse events between the two groups.

	CF(N=25)		DCF(N=30)		P-Value	
Adverse event	All grades	Grades 3/4	All grades	Grades 3/4	All grades	Grades 3/4
Neutropenia	(64%)16	(44%)11	(53%)16	(50%)15	58.	78.
Anemia	(32%)8		(36%)11		78.	
Thrombocytopenia	(12%)3	(8%)2	(20%)6	(10%)3	48.	1.00
Nausea & vomiting	(60%)15	(8%)2	(70%)21	(7%)2	57.	1.00
Constipation	(32%)8	(4%)1	(3%)1	(0%)0	008.	45.
Diarrhea	(24%)6	(0%)0	(47%)14	(27%)8	09.	006.
Alopecia	(92%)23	(24%)6	(100%)30	(60%)18	20.	01.
Phlebitis	(68%)17	(4%)1	(57%)17	(3%)1	40.	1.00
Neuropathy	(28%)7		(33%)10		77.	
LFT	(0%)0		(3%)1		1.00	
RFT	(4%)1		(7%)2		1.00	
Mocusitis	(80%)20	(12%)3	(63%)19	(20%)6	23.	48.
Febrile neutropenia	(4%)1		(27%)8		03.	
GCSF	(8%)2		(23%)7		16.	

events except for febrile neutropenia between the two groups.

In tax 323, DCF caused more leukopenia and neutropenia; however, in our study, neutropenia did not show a significant difference between the two groups while febrile neutropenia was more frequently seen in the DCF group. Severe alopecia and diarrhea was more common in the DCF group than in the CF group.

Treatment related delay in starting the second cycle at the scheduled date was more common in the CF group in comparison with the DCF group (45.8% vs. 10.7%) with a mean of 5.79 (0-14) days in the CF and 1.8 (0-14) days in the DCF group. Posner et al [7] also reported a lower rate of prolonged neutropenia for the Docetaxel containing group in TAXs 324. So, it seems DCF is more tolerable than the CF regimen.

Conclusion

We could not find any significant differences between response to DCF and CF combination chemotherapy in Iranian patients with LAHNSCC. However, for better evaluation, larger studies with better designs are being conducted in our center.

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