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ORIGINAL ARTICLE

Docetaxel and platinum combination chemotherapy in locally advanced or metastatic head and neck cancer

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Summary

Purpose: *To assess the efficacy and toxicity of the docetaxel and platinum combination in patients with locoregionally advanced or metastatic squamous cell carcinoma of the head and neck (SCCHN).*

Patients and methods: *A total of 24 patients with metastatic or locoregionally advanced SCCHN treated with docetaxel and platinum combination chemotherapy were retrospectively reviewed. All of them had histologically proven SCCHN, measurable disease and ECOG performance status of 2 or less, and were treated with docetaxel 75 mg/m^2 as a 60 min i.v. infusion on day 1, followed by cisplatin 75 mg/m^2 or carboplatin AUC 6 as a 60 min i.v. infusion on day 1 every 3 weeks, until disease progression or unacceptable toxicity. Patients were evaluated for response, survival and toxicity.*

Results: *Seven (29%) patients showed partial response (PR) and 1 (4%) complete response (CR) for an overall response rate of 33%. Twelve (50%) patients had stable disease (SD). Disease control rate was 83%. The median follow-up time was 26.4 months (range 2-127), the median time to progresion 16 months (range 2-20), and the median overal survival 19 months (range 2-22). Grade 3-4 hematologic toxicity occurred in 13 (54%) patients. Febrile neutropenia was seen in 5 (21%) patients.*

Conclusion: *Docetaxel plus cisplatin or carboplatin is an effective regimen with acceptable safety profile for palliation of locally advanced or metastatic SCCHN.*

Key words: docetaxel, head and neck cancer, platinum combination

Introduction

SCCHN is usually diagnosed in locally advanced stage [1]. Although prognosis of early-stage SCCHN is favorable with 5-year survival rates of 70-90% after standard therapy (surgery, radiotherapy, or both), about two thirds of the patients present with advanced locoregional (stage III and IV) disease. Despite aggressive initial management of the primary tumor, locoregional recurrence occurs in up to 60% and distant metastatic spread in up to 25% of these cases, with 3-year survival rate below 30% [2]. In addition, approximately 10% of the patients have distant metastases at the time of initial presentation or locoregional disease that is deemed incurable. For patients with incurable cancer at presentation or recurrent disease, either locoregionally or at distant sites, prognosis is particularly poor, with a median survival of only 6 months with conventional palliative chemotherapy. Cisplatin and 5-fluorouracil (5-FU) combination chemotherapy has demonstrated superior response rates compared with single-agent cisplatin, 5-FU, or methotrexate. Despite better response rates, combination chemotherapy including cisplatin and 5-FU does not provide overall survival advantage compared with single agents [3-7]. Administration of cisplatin and 5-FU combination chemotherapy necessitates prolonged infusion time and has significant mucosal toxicity. New combination regimens are needed.

In locoregional recurrent and metastatic SCCHN, efficacy of docetaxel was demonstrated after *in vitro*

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and *in vivo* studies [8,9]. In several clinical studies, a significant efficacy of docetaxel and cisplatin combination was demonstrated in patients with advanced SCCHN [10].

The aim of the present study was to assess the efficacy and toxicity of the docetaxel and cisplatin or carboplatin combination chemotherapy in patients with locoregionally advanced or locoregionally recurrent or metastatic SCCHN.

Patients and methods

Patients

Twenty-four patients with SCCHN were included and retrospectively reviewed. All patients were treated at the Division of Medical Oncology, Ege University School of Medicine, between 2004 and 2005. All of them had histologically proven locally advanced and/or locoregionally recurrent and distant metastatic disease. Before chemotherapy, all patients had baseline physical examination, complete blood cell count and serum biochemistry, magnetic resonance imaging of the head and neck, chest computed tomography and abdominal ultrasonography. All patients underwent meticulous physical examination and complete blood count and serum biochemistry assessment every 21 days. Radiological assessment was repeated every 3 cycles.

Treatment plan

Docetaxel 75 mg/m^2 in 500 ml 5% dextrose solution and cisplatin 75 mg/m^2 in 500 ml 0.9% NaCl solution were administered as a 60 min i.v. infusion on day 1. Cisplatin was given with creatinine clearance ≥ 60 ml/min and with pre and posthydration and mannitol diuresis. If creatinine clearance was <60 ml/min carboplatin AUC 6 in 500 ml 5% dextrose solution was administered as a 60 min infusion instead of cisplatin. Premedication with methylprednisolone 32 mg p.o. was given the night before treatment and continued on days 1-3. Prophylactic antiemetic treatment was given routinely with a 5-HT blocker prior to chemotherapy administration. Treatment courses were repeated every 21 days. Before each course complete blood cell count and serum biochemistry were obtained. Treatment was given with neutrophiles ≥1,500/μL, and platelets ≥100,000/μL. Dose reductions were planned for grade 3-4 (NCI-CTC grading system) hematologic and non hematologic toxicities other than alopecia and anemia. A maximum of 2 dose reduction levels were allowed (25% or 50%). Patients continued therapy until disease progression or unacceptable toxicity. Every 3 cycles of chemotherapy, magnetic resonance imaging of the head and neck and/or chest computed tomography were performed in order to assess tumor response.

Response evaluation

Primary endpoints were response rate and progression free survival, and secondary endpoints overall survival and toxicity. CR was defined as disappearance of all clinically detectable tumor. PR was defined as 50% or more decrease in all diameters of all measured lesions. PD was defined as 25% or more increase of the measured lesions or appearance of new lesion(s). SD was defined as disease that did not fulfill the criteria for PR or PD. Overall response rate was defined as the sum of complete and partial response. Disease control rate was defined as the sum of CR, PR and SD. Progression free survival was determined as the time interval between the beginning chemotherapy and the first objective evidence of disease progression. Overall survival was determined as the time interval between starting chemotherapy and death.

Toxicity

Patients were evaluated for hematologic and non hematologic toxicities. National Cancer Institute (NCI) Common Toxicity Criteria were used for this evaluation.

Statistical analysis

Progression free survival and overall survival were calculated with the Kaplan-Meier method. The statistical package for social sciences (SPSS) v.11.5 software was used for statistical analysis.

Results

Patients

A total 24 SCCHN patients were evaluated. Eight of 13 locoregionally recurrent patients had received chemoradiotherapy with weekly cisplatin as primary treatment. Three of 13 locoregionally recurrent patients had surgery only as their primary treatment. Two of 13 locoregionally recurrent patients had received radiotherapy only as their primary treatment. Five of 9 metastatic patients had surgery alone as their primary treatment. Two locally advanced and 4 of 9 metastatic patients had no prior treatment. Patient characteristics

are summarized in Table 1. Four (16%) patients were females and 20 (84%) males. Median age was 58 years (range 38-77). Two patients had ECOG performance status score 2, 13 had 1 and 9 had 0 score. Two patients had carcinoma of the hypopharynx, 1 of the oropharynx, 7 of the larynx, 7 of the nasopharynx, and 7 non specified head and neck cancer. Metastatic sites included lung (7 patients) and bone (2 patients). Two patients had locoregional radiotherapy, 8 patients had surgery alone and 8 patients had chemoradiotherapy with weekly cisplatin 40 mg/m^2 for their disease. No differences were seen between response rates and prior treatment modalities.

Response and survival

Response rates are summarized in Table 2. Overall response rate was 33% and disease control rate 83% (CR 1 [4%], PR 7 [29%], SD 12 [50%]). Median progression free survival was 16 months (range 2-20; Figure 1), median overall survival was 19 months (range 2-22; Figure 2). Patients received 119 (median 5, range 2-8) cycles of docetaxel and cis/carboplatin. Only 9 cycles with carboplatin were administered.

Toxicity

Hematologic and non hematologic toxicities are summarized in Table 3. Grade 3-4 hematologic toxicity was experienced by 13 (54%) patients. Febrile neutropenia occurred in 5 (20%) patients. Grade 3 mucositis was experienced by 1 (4%) patient, whereas 3 (12%) patients had grade 3-4 nausea-vomiting. Grade 3 neuropathy was experienced by 1 (4%) patient after 3 cycles; because of this treatment was discontinued.

Table 1. Patient, disease and prior treatment characteristics

Characteristic	*Patients, n*	*%*
Sex		
Male	20	84
Female	4	16
Age (years)		
Median	58	
Range	38-77	
ECOG performance status		
0	9	37
1	13	55
2	2	8
Primary tumor site		
Hypopharynx	2	8
Oropharynx	1	5
Larynx	7	29
Nasopharynx	7	29
Head & neck, unspecified	7	29
Recurrence site		
Locally advanced	2	8
Locoregional recurrence	13	55
Metastatic	9	37
Prior therapy		
Radiotherapy	2	8
Surgery	8	33
Radiotherapy+chemotherapy	8	33

Table 2. Response rates

Response	*Patients, n*	*%*
Complete response	1	4
Partial response	7	29
Stable disease	12	50
Progressive disease	4	17
Overall response	8	33
Disease control	20	83

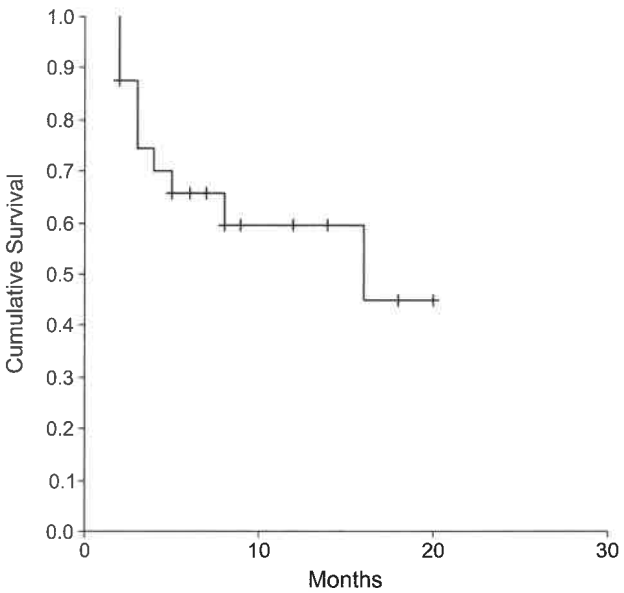


Figure 1. Progression free survival.

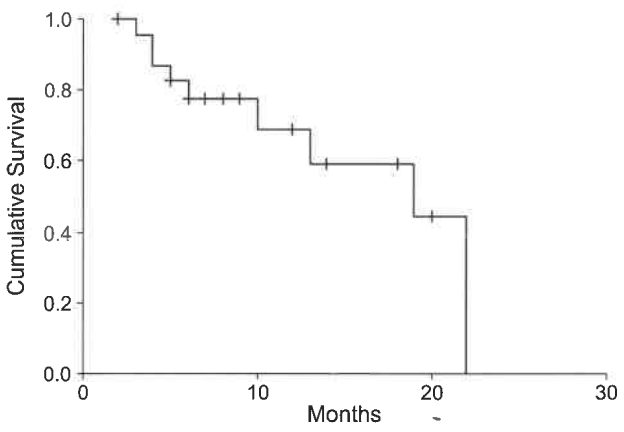


Figure 2. Overall survival.

Discussion

In this study the efficacy and toxicity of docetaxel and platinum combination chemotherapy has been evaluated in locoregionally recurrent, locally advanced and metastatic SCCHN. The efficacy of paclitaxel and docetaxel in SCCHN has been demonstrated in many studies [8,11]. Single-agent docetaxel had produced similar results when compared with the standard cisplatin and 5-FU combination chemotherapy in SCCHN. Catimel et al. have found 32% overall response rate with docetaxel in a similar patient population [8]. Dreyfuss et al. have reported 13% CR, 29% PR and 29% SD with single-agent docetaxel administered in locally advanced and metastatic SCCHN except nasopharyngeal cancer [9].

In *in vitro* experiments with various cell lines no cross resistance between docetaxel and cisplatin has been shown [12,13]. Glisson et al. administered docetaxel and cisplatin combination chemotherapy to patients with recurrent or metastatic SCCHN. Patients were chemotherapy-naïve or had received one prior regimen as neoadjuvant or concurrent treatment with radiation. Overall survival was 9.6 months [10]. Specht et al. reported 32% overall response rate with the same doses as in our study of docetaxel and cisplatin in SCCHN patients. Median survival was 11 months [14]. Gedlicka et al. evaluated the efficacy of docetaxel and cisplatin in SCCHN patients except recurrent or metastatic nasopharyngeal cancer and found 17% CR and 35% PR rate. Overall survival was 11 months [15]. Posner et al. administered 5-FU, cisplatin and docetaxel combination to 43 chemotherapy-naïve patients with locally advanced SCCHN except nasopharyngeal cancer. A 40% CR rate was reported. However, 95% of the patients suffered grade 3-4 neutropenia and 19% of them developed febrile neutropenia [16]. In the study of Chua et al. docetaxel and cisplatin combination chemotherapy was administered to patients with metastatic nasopharyngeal cancer. There were 56.3% PRs and 6.3% CRs. Median survival was 12.4 months [17]. In another study McCarthy et al. found a 22% PR rate in recurrent and metastatic SCCHN patients who were treated with docetaxel and cisplatin. Time to progression was 8.4 months and 1-year overall survival 76% [18].

Table 3. Grade 3-4 toxicities

Toxicity	*Patients, n*	*%*
Neutropenia	13	54
Febrile neutropenia	5	20
Stomatitis	1	4
Nausea-vomiting	3	12
Neuropathy	1	4

In this study, patients with nasopharyngeal cancer and locally advanced SCCHN who had been treated with induction chemotherapy with docetaxel and cisplatin followed by radiotherapy were also enrolled. In our study we attained a 33% objective response rate (29% PR, and 4% CR). Overall survival was 19 months. As for severe toxicity we registered 54% grade 3-4 neutropenia and 20% febrile neutropenia cases. Glisson et al. reported that grade 4 neutropenia and febrile neutropenia were observed in 71% and 6% of patients, respectively [10]. Specht et al. reported that grade 3-4 neutropenia was detected in 75% of their patients [14] and Catimel et al. reported grade 3-4 neutropenia in 61% of the chemotherapy courses [14]. Comparable toxicity results were seen in our study. If we look at the literature we see that the response rates in our study were similar with similar patient groups compared with those seen in the groups of single-agent docetaxel and docetaxel plus cisplatin combination, but in our study overall survival was longer. This result may be explained taking into consideration the good performance status of patients or the presence of nasopharyngeal cancer patients in our study group or the presence of a subgroup of patients given docetaxel and cisplatin as induction chemotherapy. Comparing docetaxel and cisplatin combination with triple-agent chemotherapy regimens like docetaxel, cisplatin and 5-FU or paclitaxel, ifosfamide and carboplatin, the response rates of our study are lower [16,19]. However, if we look at the toxicity profiles of triple-agent combination regimens, the hematologic toxicities, like grade 3-4 neutropenia and febrile neutropenia, are much higher than those observed in our study.

In this study grade 3-4 neutropenia was observed in 54% of the patients. Shin et al. reported that grade 3-4 neutropenia was detected in 92% of their patients treated with paclitaxel, carboplatin and ifosfamide [19], while in the study by Posner et al. grade 3-4 neutropenia was detected in 95% of patients treated with docetaxel, cisplatin and 5-FU [16].

We conclude that docetaxel and platinum combination chemotherapy is effective and tolerable for locally advanced, recurrent and metastatic SCCHN patients.

References

1. Fleming ID, Cooper JS, Henson DE et al. AJCC Cancer staging handbook. AJCC Cancer Staging Manual. Philadelphia, PA, Lippincott Williams & Wilkins, 1998.
2. Posner MR, Haddad RI, Wirth L et al. Induction chemotherapy in locally advanced squamous cell cancer of the head and neck: evolution of the sequential treatment approach. Semin Oncol 2004; 31: 778-785.

3. Campbell J, Dorman E, McCormick M et al. A randomised phase III trial of cisplatinum, methotrexate, cisplatinum+methotrexate and cisplatinum+5-fluorouracil in end stage head and neck cancer. Acta Otolaryngol 1987; 103: 519-528.
4. Clavel M, Vermorken J, Cognetti F et al. Randomised comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck: A phase III study of the EORTC Head and Neck Cancer Cooperative Group. Ann Oncol 1994; 5: 521-526.
5. Jacobs C, Lyman G, Velez-Garcia E et al. A phase III randomised study comparing cisplatin and fluorouracil as single agents or in combination for advanced squamous cell carcinoma of the head and neck. J Clin Oncol 1992; 10: 257-263.
6. Forastiere AA, Metch B, Schuller D et al. Randomised comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous cell carcinoma of the head and neck: A Southwest Oncology Group study. J Clin Oncol 1992; 10: 1245-1251.
7. Liverpool Head and Neck Oncology Group: A phase III randomised trial of cisplatinum, methotrexate, cisplatinum plus methotrexate and cisplatinum plus 5-fluorouracil in end stage squamous cell carcinoma of the head and neck . Br J Cancer 1990; 61: 311-315.
8. Catimel G, Verwej J, Mattijssen V et al. Docetaxel (Taxotere): An active drug for the treatment of patients with advanced squamous cell carcinoma of the head and neck : EORTC Early Clinical Trials Group. Ann Oncol 1994; 5: 533-537.
9. Dreyfuss AI, Clark JR, Norris CM et al. Docetaxel: An active drug for squamous cell carcinoma of the head and neck. J Clin Oncol 1996; 14: 1672-1678.
10. Glisson BS, Murphy BA, Frenette G et al. Phase II trial of docetaxel and cisplatin combination chemotherapy in patients with squamous cell carcinoma of the head and neck. J Clin Oncol 2002; 20: 1593-1599.
11. Forastiere AA. Paclitaxel (Taxol) for the treatment of head and neck cancer. Semin Oncol 1994; 21 (Suppl 8): 49-52.
12. Hill BT, Whelan RDH, Shellard SA et al. Differential cytotoxic effects of docetaxel in a range of mammalian tumor cell lines and certain drug resistant sublines in vitro. Invest New Drugs 1994; 12: 169-182.
13. Kelland LR, Abel G. Comparative in vitro cytotoxicity of taxol and taxotere against cisplatin sensitive and resistant human ovarian carcinoma cell lines. Cancer Chemother Pharmacol 1992; 30: 444-450.
14. Specht L, Larsen SK, Hansen HS. Phase II study of docetaxel and cisplatin in patients with recurrent or disseminated squamous cell carcinoma of the head and neck. Ann Oncol 2000; 11: 845-849.
15. Gedlicka C, Formanek M, Selzer E. Phase II study with docetaxel and cisplatin in the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck. Oncology 2002; 62: 145-150.
16. Posner MR, Glisson B, Frenette G et al. Multicenter phase I-II trial of docetaxel, cisplatin, and fluorouracil induction chemotherapy for patients with locally advanced squamous cell cancer of the head and neck. J Clin Oncol 2001; 19: 1096-1104.
17. Chua DTT, Sham JST, Au GKH. A phase II study of docetaxel and cisplatin as first line chemotherapy in patients with metastatic nasopharyngeal carcinoma. Oral Oncol 2005; 41: 589-595.
18. McCarthy JS, Tannock IF, Degendorfer P et al. A phase II trial of docetaxel and cisplatin in patients with recurrent or metastatic nasopharyngeal carcinoma. Oral Oncol 2002; 38: 686-690.
19. Shin DM, Khuri FR, Glisson BS et al. Phase II study of paclitaxel, ifosfamide, and carboplatin in patients with recurrent or metastatic head and neck squamous cell carcinoma. Cancer 2001; 91: 1316-1323.