RESEARCH ARTICLE

# Efficacy and Safety of Concomitant Chemoradiotherapy with Cisplatin and Docetaxel in Patients with Locally Advanced Squamous Cell Head and Neck Cancers

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## Abstract

**Background: Chemoradiation (CRT) using cisplatin-based regimens has become the standard of care in the treatment of squamous cell head and neck cancers (SCHNC). The impact of taxanes as radiosensitizing agents with concurrent CRT regimens is unknown. We therefore retrospectively evaluated the efficacy and tolerability of a weekly cisplatin+docetaxel combination with CRT in locally advanced SCHNC. Methods: Sixty-six patients with locally advanced SCHNC (39.4% stage IV, 53% stage III, and 7.6% stage II) were assessed retrospectively. Total radiation dose to the PTV of gross disease (primary and/or node) was 70 Gy/ 35 fractions, 5 fractions per week. Minimum doses of 60 Gy and 50 Gy were administered to PTVs of elective high risk and low risk disease, respectively. Chemotherapy (CT) consisted of weekly cisplatin (20 mg/m$^2$)+docetaxel (20 mg/m$^2$) concurrently with RT. Results: The median age of the patients was 58 years (range, 32-77). Objective response rate was 83.3%. The 2-year progression-free survival (PFS) and overall survival (OS) were 75.7% and 78.3%, respectively. The most common grade 3 and 4 toxicities were mucositis (36.4%), nausea and vomiting (12.1%), neutropenia (4.5%). Conclusion: Weekly cisplatin and docetaxel concurrent with RT for locally advanced SCHNC was found tolerable with high efficacy.**

**Keywords:** Squamous cell head and neck cancers - chemoradiotherapy - cisplatin - docetaxel - safety

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## Introduction

Head and neck cancers comprise 3% of the newly diagnosed cancer patients in the USA. It is thought that 49.260 new cases with oral cavity, pharynx and larynx cancers developed in 2010 and 11.480 deaths were recorded (Jemal et al., 2010). Squamous cell cancers comprise 90% of the head and neck tumours. Alcohol and tobacco use is the most significant etiological factor at oral cavity, oropharynx, hypopharynx and larynx cancers (Landis et al., 1999). Another risk factor at oropharynx squamous cell cancer development is human papilloma virus (HPV) infections (D'Souza et al., 2007).

Of the patients, 30-40% is stage I and Stage II, and the radiotherapy applied alone or surgery treatment is recommended. There is no difference between these treatments for the early stage patients in terms of survival. However 60-70% of the patients consult at the local advanced stage of the disease. Despite radical surgery and/or radiotherapy at patients, survival rates for 5 years are below 30% (Pignon et al., 2000). In the past 20 years, distant metastasis development has decreased with combined treatment approaches and there has become an increase at the control of the disease and survival (Bourhis et al., 2007).

Currently many studies comparing radiotherapy applied alone and combined chemotherapy treatment concomitantly or sequentially and metaanalysis at advanced stage disease showed that combined therapy is superior to radiotherapy alone in terms of overall survival, disease free survival and local control (Brizel et al., 1998; Wendt et al., 1998; Jeremic et al., 2000; Adelstein et al., 2003; Pignon et al., 2007; Forastiere et al., 2013; Haddad et al., 2013; Huang et al., 2013). Even though there becomes an increase at local control and overall survival with the combination with cisplatin based

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regimens or cetuximab and radiotherapy, it is still not clear which chemotherapy regiment is optimal treatment. There have been studies trying to find answers to the questions whether a single or multi agent chemotherapy should be used with radiotherapy and which radiotherapy program should be used (conventional or IMRT). In addition, there is an uncertainty over the place of induction chemotherapy at the patients applied concurrent chemoradiotherapy and of the adjuvant neck dissection and adjuvant chemotherapy at the patients having bulky adenopathy after CRT. Depending on the studies carried out, it is clear that cisplatin applied alone and the combination of cisplatin with fluorourasil have been used in the concomitant CRT treatment and cetuximab has taken its place in concomitant CRT in recent years (Bernier et al., 2007; Bourhis et al., 2010; Huang et al., 2013). Also, some stage I and stage II studies have been carried out regarding a combined usage of platin and taxanes at concomitant CRT recently. Addition of taxanes to cisplatin increased the antitumoral efficacy of concomitant treatment (Mauer et al., 1998; Tishler et al., 2002; Suzuki et al., 2003; Mencoboni et al., 2005; Tsao et al., 2006; Haddad et al., 2013). In the light this data, the current study aimed at investigating the efficacy and safety of concomitant cisplatin and docetaxel treatment with radiotherapy at locally advanced squamous cell carcinoma of the head and neck.

## Materials and Methods

*Patients*

The files of 66 patients (8 woman, 58 men) with local advanced stage SCHNC treated with cisplatin and docetaxel combination concurrent with RT were assessed retrospectively. Patients with distant organ metastases at diagnosis were excluded. Patients were staged based on clinical findings and imaging methods according to American Joint Committee on Cancer (AJCC) TNM staging system for the head and neck cancers (7$^{th}$ Edition, 2010).

*Treatment*

The patients were treated supine and immobilized using a thermoplastic mask with a head rest. CT images for the treatment planning were obtained at 2-5 mm intervals from the vertex to below the carina. The CT data was loaded into the Eclipse TPS. Gross tumor volumes of the primary (GTV-T) and all macroscopic nodal metastases (GTV-N) were delineated on each CT slice after reviewing available clinical data including diagnostic CT and /or MRI and/or PET-CT images. CTVs were defined as the volume encompassing GTV with a 10 mm margin in all directions. Elective clinic volume-High risk (CTV-Eh) defined as areas close to the GTV at high risk for microscopic disease (eg. Margins around the primary, the whole lymph node level in which lymph node metastases have been found, possibly also the next lymph node level below the level of metastases). Elective CTV-low risk (CTV-El) defined as volumes judged to be at lower but still significant risk of microscopic disease (uninvolved lymph node levels II, III, IV, V, retropharyngeal). All of the CTVs were subsequently expanded automatically in 3D by 3-5 mm to create the related PTVs. Total radiation dose to the PTV of gross disease (primary and/or node) was 70 Gy/35 fractions, 5 fractions per week. Minimum dose of 60 Gy and 50 Gy were administered to PTVs of elective high risk and low risk disease, respectively. All of the target volumes were individualized to exclude air cavities, periosteum and compartmental fascia without evidence of tumor invasion. Organs at risk were routinely outlined on the planning CT images. Maximum doses of 45 Gy and 54 Gy for the spinal cord and brain stem were allowed respectively. A photon of 6 MV was used for the irradiation and electron fields in various energies were added to cover the involved lymph nodes close to the spinal cord. During the treatment, patients were assessed through physical examination, complete blood count and serum biochemistry. Evaluation in terms of toxicity was made depending on Common Toxicity Criteria for Adverse Events 3.0. Two months after chemotherapy treatment, patients were evaluated through the methods of physical examination and imaging in terms of treatment response. The patients were followed up as every 3 months in the first 2 years and every 6 months in the 3-5 years through the methods of physical examination and imaging.

*Statistical Analysis*

Survival analyses were performed using Kaplan-Meier method. Progression-free survival (PFS) was defined as the time from diagnosis to disease relapse or death. Similarly, overall survival (OS) was calculated as the time elapsed from the date of diagnosis to the date of death or the last visit. Statistical analyses were carried out using SPSS 15.0 program.

## Results

*Patients*

The median age of the patients were 58 (32-77) and median follow up duration were 16.5 months (2.3-58.5). The characteristics of the patients were summarized in Table 1. As for the stages, 39.4% of the patients were stage IV, 53% were stage III, and 7.6% were stage II. The distribution of the patients according to tumour area was: larynx (n=47), hipopharynx (n=5), oropharynx (n=6), and oral cavity (n=8). Eight patients were given CRT after induction CT, 8 patients were applied adjuvant CT after CRT and 50 patients were applied CRT alone.

Forty-one patients (64.2%) were able to receive all the planned weekly CT doses. The remaining patients were given 4 weeks (13.6%) and 5 weeks (10.6%) of the planned CT. All of the patients were able to complete the planned RT schedule.

*Efficacy*

The responses obtained after CRT are as follows; 47 patients achived complete response (CR) and 5 partial response (PR), 3 patients had stable disease (SD), 2 patients had progressive disease (PD). Response assessment was not carried out in nine patient. During the follow-up period, local recurrence occurred at 7 patients and metastasis developed with local recurrence at 7 patients (n=2 bone, n=4 lung, n=3 liver, n=1 brain). Five

patients having local recurrence were applied surgery. The median progression free survival (PFS) and overall survival (OS) has not been reached yet. Two-year PFS was 75.7% (Figure 1) and OS 78.3% (Figure 2).

*Toxicity*

Treatment related acute toxicities were summarized in Table 2. However, grade 3-4 toxicities were not uncommon and included mucositis (36.4%), nausea and vomiting (12.1%), neutropenia (4.5%). Six patients were developed grade 3-4 infection (oesophageal candida n=2, febrile neutropenia n=1, pneumonia n=4), 1 patient was developed grade 4 nephrotoxicity, 2 patients were developed grade 1-2 hepatotoxicity, and 2 patients, grade 3 weight loss developed. As 1 patient developed myocardia infarction at the 3rd week of the chemoradiotherapy, the treatment was terminated. Treatment-related death was observed in two patients due to sepsis and exacerbation of chronic obstructive pulmonary disease.

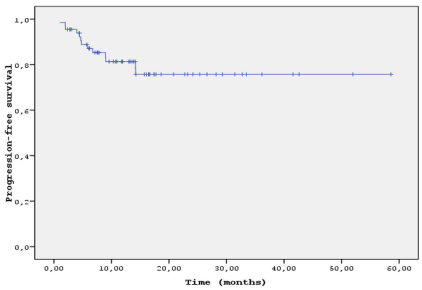


**Figure 1. Progression-Free Survival**

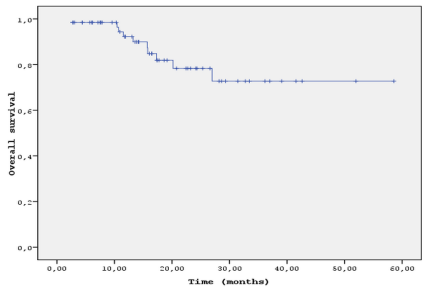


**Figure 2. Overall Survival**

**Table 1. Characteristics of the Patients**

| | | N (%) |
|---|---|---|
| Tumour area | Larynx | 47 (71.2) |
| | Hipopharynx | 5 (7.6) |
| | Oropharynx | 6 (9.1) |
| | Oral cavity | 8 (12.1) |
| Stage | 2 | 5 (7.6) |
| | 3 | 35 (53.0) |
| | 4A | 20 (30.3) |
| | 4B | 6 (9.1) |
| Tumour diameter (T) | 2 | 18 (27.3) |
| | 3 | 35 (53.0) |
| | 4a | 9 (13.6) |
| | 4b | 4 (6.1) |
| Lymph node involvement (N) | 0 | 26 (39.4) |
| | 1 | 15 (22.7) |
| | 2 | 21 (31.8) |
| | 3 | 4 (6.1) |
| Induction CT | Yes | 8 (12.0) |
| | No | 58 (88.0) |
| Adjuvant CT | Yes | 8 (12.0) |
| | No | 58 (88.0) |

**Table 2. Treatment Related Acute Toxicities (Grade ≥3)**

| Toxicity | Grade 3 N (%) | Grade 4 N (%) | Grade 5 N (%) |
|---|---|---|---|
| Mucositis | 17 (25.8) | 7 (10.6) | 0 |
| Nausea – vomiting | 7 (10.6) | 1 (1.5) | 0 |
| Neutropenia | 1 (1.5) | 2 (3.0) | 0 |
| Anaemia | 0 | 0 | 0 |
| Thrombocytopenia | 0 | 0 | 0 |
| Infection | 3 (4.5) | 3 (4.5) | 1 (1.5) |
| Hepatotoxicity | 0 | 0 | 0 |
| Nephrotoxicity | 0 | 1 (1.5) | 0 |
| Cardio-toxicity | 0 | 1 (1.5) | 0 |
| Asthenia | 0 | 0 | 0 |
| Weight loss | 1 (1.5) | 0 | 0 |
| Dermatitis | 0 | 0 | 0 |
| Cerebrovascular event | 0 | 0 | 0 |
| Pulmonary toxicity | 0 | 0 | 1 (1.5) |

## Discussion

CRT has been increasingly used in the head and neck cancers for the last 30 years. After 2000s, the rate of overall survival at the head and neck cancers with concomitant CRT increased. After the emergence of these data, concomitant CRT treatment with platinum containing regimens particularly at the treatment of unresectable head and neck cancers has been used as an effective treatment (Adelstein et al., 2000; Pignon et al., 2000; Forastiere et al., 2003; Forastiere et al., 2013, Haddad et al., 2013). The meta-analysis (MACH-NC) evaluating the addition chemotherapy with various multimodality treatment (induction treatment, adjuvant treatment after surgery or radiotherapy or concomitant radiotherapy) at the locally advanced SCHNC was reported that most benefit was obtained with concomitant chemoradiotherapy and an increase of 8% was obtained at 5-year overall survival (Pignon et al., 2000). In other studies comparing concomitant chemoradiotherapy (chemotherapies including cisplatin and fluorouracil infusion) and RT alone were reported a better overall survival was obtained concomitant chemoradiothreapy at locally advanced head and neck cancers (Brizel et al., 1998; Wendt et al., 1998; Calais et al., 1999; Forastiere et al., 2013, Haddad et al., 2013, Huang et al., 2013).

In many studies, either different radiotherapy schemes, whether standard or concomitant with hyperfraction radiotherapy, or addition of them to successive chemotherapy have been investigated. Nevertheless, how optimal treatment must be at local advanced SCHNC should be discussed. Very good response rates have been obtained at phase 1-2 clinical studies regarding the use of docetaxel as the only agent at concurrent chemoradiotherapy (Matsumoto et al., 2006; Tishler et al., 2006; Okami et al., 2008; Mencoboni et al., 2011; Huang et al., 2013). Overall response rates (ORR) at these studies varies from 86-90%. Matsumato et al.'s study carried out 25 patients with locally advanced SCHNC, 10 mg/

$m^2$/weekly docetaxel was given concomitantly with RT and OS for 2 years was given as 47.3% (Matsumoto et al., 2006). In their study, Okami et al. (2008) 10 mg/$m^2$/ weekly docetaxel was given concomitantly with RT and DFS for 5 years was reported as 90%.

In the studies where docetaxel combined with platinum at concomitant chemoradiotherapy, ORR varied from 74-100% (Karasawa et al., 2002; Schwartz et al., 2005; Tsao et al., 2006; Chitapanarux et al., 2011). OS for two years were reported as 65% (25-26), DFS for 2 years were 63% (Chitapanarux et al., 2011) and PFS for 2 years were 61% (Tsao et al., 2006). ORR in our study was 78.8% and similar to the one in the literature. OS rates for 2 years were 78.3% and PFS rates for 2 years were found as 75.7% respectively and were much better compared to those in the literature.

Grade 3-4 toxicities in the studies of concurrent chemoradiotherapy with docetaxel and platinum in the literature mucositis 14-81%, dysphagia 13-50%, nausea and vomiting 6%, weight loss 12%, neutropenia 1-14% and anemia were reported and thrombocytopenia were not observed (Karasawa et al., 2002; Schwartz et al., 2005; Matsumoto et al., 2006; Tsao et al., 2006; Chitapanarux et al., 2011). In our study, grade 3-4 toxicities rates were similar in the literature; mucositis 36.4%, nausea and vomiting 12.1%, weight loss 1.5%, neutropenia 4.5% and grade 3-4 anemia and thrombocytopenia were not observed.

Local control rates, overall response rates and survival outcomes were better than the reported studies in the literature.

As a conclusion, weekly cisplatin and docetaxel regimen concomitant with radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck were found effective, tolerable and safety. Local control rates, overall response rates and survival outcomes were better than the reported studies in the literature. However, there is a need for large scaled prospective controlled studies.

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