Hyperfractionated Radiotherapy with Concurrent Docetaxel for Advanced Head and Neck Cancer: A Phase II Study

KUMIKO KARASAWA1,2, FUMIHIKO MATSUMOTO3, SIN ITO3, SINICHI OBA3, TOMOHISA FURUYA4, HISAKO HIROWATARI2, HIROMI IZAWA4, KANA ITO2 and KEISUKE SASAI2

1Research Center Hospital for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan; 2Department of Radiology, Faculty of Medicine, Juntendo University, Tokyo, Japan; 3Department of Otolaryngology, Faculty of Medicine, Juntendo University, Tokyo, Japan; 4Department of Radiology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

Abstract. Aim: To evaluate the value of hyperfractionated radiotherapy with concurrent use of low-dose docetaxel in locally-advanced head and neck squamous cell cancer (HNSCC). Patients and Methods: Patients eligible for this study had confirmed diagnosis of HNSCC stages II (>10 cm³) to IVB. Radiotherapy was delivered twice daily at 1.2 Gy/fraction to a total dose of 72.0 Gy. Docetaxel (10 mg/m²) was administered weekly during radiotherapy. Results: From March 2003 to October 2008, 70 patients were treated. Primary sites included the oropharynx (n=25), hypopharynx (n=24), larynx (n=18), and other sites (n=3). Major grade 3 acute toxicities included mucositis (n=43) and treatment-related pain (n=20). The median follow-up period for surviving patients was 43 months. The 5-year local control rate and overall survival rate were 62.6% and 61.6%, respectively. Conclusion: This modality is a valuable treatment option for the management of locally-advanced HNSCC.

Tumor control with functional organ preservation is a desirable goal in the treatment of head and neck malignancies. For advanced cancer, concurrent chemoradiotherapy improves locoregional control and survival compared with radiotherapy alone. In a recent meta-analysis comparing chemoradiotherapy and radiotherapy alone for head and neck cancer, 5-year survival improved by 8% and cisplatin was the most effective drug for concurrent single-agent use (1). Taxanes are active agents useful for chemoradiation of head and neck squamous cell carcinoma (HNSCC) (2, 3) owing to their radiosensitizing effect (4). They stabilize microtubules and lead to cancer cell cycle arrest in the radiosensitive G2/M phase (4, 5). Docetaxel exhibits a radiosensitizing effect 10-times higher than that of paclitaxel at equimolar concentrations in tumor cell lines (5). However, the optimal regimen of docetaxel combined with radiotherapy has not been clearly established.

Altered fractionated radiotherapy is another effective method of increasing tumor control. One meta-analysis of 15 trials confirmed the effectiveness of accelerated or hyperfractionated radiotherapy (HFRT) in head and neck cancer (6). HFRT using 1.2 Gy twice daily has been widely studied at the University of Florida and the Radiation Therapy Oncology Group conducted dose-finding studies demonstrating that locoregional control improved with increasing total doses of 67.2, 72.0 and 76.8 Gy (7). We reported a total dose of 1.2 Gy twice daily, up to a total dose of 72.0 Gy with concurrent chemotherapy (8). Several studies demonstrated that HFRT with concurrent chemotherapy is superior to HFRT alone (9-17).

We had conducted a phase I/II study of concurrent docetaxel and carboplatin administration (18). This platinum-based chemotherapy agent combined with taxanes and conventional radiotherapy resulted in an intense radiosensitizing effect and an 81% complete response (CR) rate and to a 94% one-year overall survival (OS) rate, although 69% of patients experienced grade 3 mucositis (18). To reduce the acute toxicity level without compromising the administration and effectiveness of this combined therapy, this phase II study of HFRT with concurrent docetaxel for advanced head and neck cancer was conducted. In an initial report, 64% of grade 3 mucositis, 88% CR and 47% two-year OS were observed (19). This article is the final report of this phase II study.

Correspondence to: Kumiko Karasawa, Research Center Hospital for Charged Particle Therapy, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba-city, Chiba 263-8555, Japan. Tel: +81 432063306 ext.6208, Fax: +81 432566506, e-mail: kkarasaw@nirs.go.jp

Keywords: Hyperfractionated radiotherapy, head and neck cancer, concurrent chemotherapy, chemoradiotherapy.
Patients and Methods

Eligibility. Patients were eligible for this study if they met the following inclusion criteria: histologically-proven squamous cell carcinoma of the head and neck of clinical stage II (tumor volume >10 cm³), III, IVA or IVB according to the 2002 staging criteria of the International Union Against Cancer (UICC) (20), no previous treatment, performance status according to the criteria of the Eastern Cooperative Oncology Group (ECOG) ≥1 and no major impairment of the liver, kidney, bone marrow, lung or heart function. Laboratory data enrollment included the following: a neutrophil count of ≥2,000/mm³, platelet count ≥100,000/mm³, creatinine clearance (CrCl) >50 ml/min, alkaline phosphatase levels of <2.5 times UNL, and total bilirubin <UNL. Evaluation included medical history, physical examination, endoscopic examination of the laryngopharyngeal area, magnetic resonance imaging (MRI) of the head and neck, computed tomography (CT) of the head and neck, chest and abdomen, and endoscopic examination of the upper digestive tracts before treatment. Fluorodeoxyglucose positron emission tomography (FDG-PET) was conducted in some cases in which it was thought to be helpful to distinguish clinical stage. Patients were excluded if they had other active cancer or a history of radiotherapy in the tumor region. Patients were informed about treatment methods, expected results and potential adverse effects. Written informed consent was obtained before treatment.

Radiotherapy. HFRT was delivered five days per week with a 4-MV photon beam of Varian Clinic 21 instrument (Varian Medical Systems, Palo Alto CA, USA) at 1.2 Gy/fraction with more than 6 h interval between sessions to a total dose of 72.0 Gy. The initial radiation field including the prophylactic regional lymph node region of the primary site was reduced after 40.8 Gy. Boost irradiation was administered to the primary lesion and metastatic lymph nodes. All radiotherapy was delivered using non intensity-modulated radiotherapy (IMRT), three dimensional conformal radiotherapy technique was planned with the Eclipse Treatment Planning System (Varian Medical Systems).

Chemotherapy. Results of our previous study suggested 10 mg/m² to be the maximum tolerable weekly dose of Docetaxel during HFRT (18). Patients in this study received six cycles of Docetaxel at doses of 10 mg/m², weekly during HFRT. Docetaxel was diluted in a 250-ml solution of 5% glucose and infused for 1 h prior to afternoon radiotherapy. Antihypersensitivity medications were administered prior to chemotherapy in patients with a history of allergic reactions.

Evaluation. Serial clinical examinations were performed in all patients to evaluate their tumor response and acute toxic reactions. Response was assessed at one month after treatment completion by physical examination, CT, MRI and FDG-PET. CR was defined as complete clinical and radiological disappearance of the tumor. Partial response (PR) was defined by a minimum 50% reduction in the product of the longest perpendicular diameter of the most easily measurable or largest tumor mass within the irradiation field. Stable disease (SD) was characterized as a reduction of <50% or a progression of <25%. Progressive disease (PD) was characterized as a progression of >25%. Local control was defined as tumor control within the irradiation field.

Table I. Patients’ and tumor characteristics.

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Age years (median)</th>
<th>Gender</th>
<th>Primary site</th>
<th>T stage</th>
<th>N stage</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>32-82 (66)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>63 (90)</td>
<td></td>
<td>Oropharynx</td>
<td>T1</td>
<td>N0</td>
<td>II (&gt;10 cm³)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (10)</td>
<td></td>
<td>Hypopharynx</td>
<td>T2</td>
<td>N1</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Larynx</td>
<td>T3</td>
<td>N2</td>
<td>IVA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral cavity</td>
<td>T4</td>
<td>N3</td>
<td>IVB</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Primary unknown</td>
<td>Tx</td>
<td>(primary unknown)</td>
<td></td>
</tr>
</tbody>
</table>

Acute toxicities were assessed weekly and graded according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) (21). Late treatment-related toxicities were graded according to the Radiation Therapy Oncology Group/ European Organization of Research and Treatment of Cancer’s Late Effect Normal Tissue (LENT/SOMA) scores (22). Statistical analysis of local control rate (LCR) and survival rate were calculated using the Kaplan–Meier method.

Results

Patients. From March 2003 to October 2008, 70 patients were treated at the Juntendo University Hospital according to the above mentioned regimen. Patient ages ranged from 32 to 82 years (median=66 years), and 63 (90%) patients were male. Primary sites included the oropharynx (n=25), hypopharynx (n=24), larynx (n=18), and oral cavity (n=1), in two cases the primary site was unknown. Stage II (n=11), stage III (n=16), IVA (n=35) and stage IVB (n=8) were included. The tumors in which the primary site was unknown were staged by nodal status (Table I).

Compliance with treatment. HFRT of 72 Gy was completed in all patients. Overall treatment time ranged from 40 to 52 days (median=43 days). The most common acute toxicity was mucositis. Mucositis and treatment-related pain above grade 3 were observed in 43 (61%) and 20 (29%) patients, respectively. Docetaxel administration frequency was reduced due to grade 3 mucositis in 21 (30%) patients. Other grade 3 non-hematological toxicities included dermatitis (n=2, 3%),...
nausea (n=2, 3%), and salivary gland dysfunction (n=2, 3%). Grade 3 hematological toxicities included leukocytopenia (n=2, 3%), neutropenia (n=2, 3%) and lymphocytopenia (n=1, 1%) (Table IIa).

Treatment response. CR was achieved in 55 patients (79%), and PR was reached in 13 patients (19%). PR was not achieved in two patients with N3 HNSCC. The median follow-up period for surviving patients was 43 months (range=2-96 months). Relapse or recurrence was observed in 30 patients (43%). Infield recurrence was observed in 19 patients (27%) and distant metastasis occurred in 12 patients (17%) a the initial recurrent site. In one patient, the primary lesion recurred and distant metastasis occurred at the same time. With regard to salvage treatment, 6 patients underwent surgery, 3 underwent radiotherapy and 27 underwent chemotherapy. Salvage surgery was successful in 2 patients with neck lymph node recurrence and 1 patient with marginal recurrence but was unsuccessful in the 3 other patients. Salvage radiotherapy was successful in 2 patients with neck lymph node recurrence, but no salvage chemotherapy was successful in any patient.

Late toxicities. The most prominent late toxicity was xerostomia, which is usually prolonged and can be severe after bilateral parotid region irradiation. Xerostomia of grade 2 and 3 was observed in 25 (36%) and 4 (6%) patients, respectively. Grade 2 laryngeal edema was evidenced in 1 patient. No other severe late toxicities were observed (Table IIb).

Survival. Eight patients developed secondary malignancies in the esophagus (n=4), oropharynx (n=1), lung (n=1), liver (n=1), and prostate (n=1). At the point of March 2012, 24 patients have died (19 from cancer and 5 from concurrent disease), 11 patients are living with disease and 40 patients are disease-free survivors. The 2-year and 5-year OS rates in this study were 70.0% and 61.1%, respectively. The LCR was 72.5% and 62.6% at 2 and 5 years, respectively (Figure 1, Table III). Significant prognostic factors for 5-year LCR were the primary site (80.1% in the oropharynx, 78.6% in larynx and 45.8 % in the hypopharynx), and clinical stage (79.8% in stage II-III, 51.5% in stage IVA, and not reached in stage IVB). Significant prognostic factors in 5-year cause-specific survival (CSS) rates were the primary site (57.4% in the hypopharynx, 78.6% in the oropharynx, and 89.9% in the larynx), and clinical stage (91.5% in stage II-III, 58.6% in stage IVA, and not reached in stage IVB) (Table III).

Discussion

HFRT with concurrent chemotherapy is the standard of care for advanced HNSCC (9-17). Comparison between the results of major trials of altered fractionated radiotherapy with concurrent chemotherapy and those of the present study is shown in Table IV. Most existing studies used platinum-based chemotherapy concurrent with HFRT on the basis of the effectiveness of previous clinical results.

In recent years, the most common combination chemotherapy regimen for advanced HNSCC has been cisplatin, 5-fluorouracil and a taxan. Based on these trends, using a taxan instead of cisplatin could be one option in concurrent chemoradiotherapy. The combination with a taxan may produce an advantage in having a strong
Radiosensitizing effect (2, 3). Taxanes have been suggested to enhance the effects of radiotherapy by causing cell cycle synchronization in the most radiosensitive G2/M phase of the cell cycle, and by activating a number of genes (4, 5). The present study demonstrated efficacy of low-dose (10 mg/m^2) weekly docetaxel comparable with that of platinum-based concurrent chemotherapy. This protocol has the merits that only a low dose of docetaxel is required, hydration is less necessary than with cisplatin, and it is usable in outpatient clinics for patients with poor renal function as well as for elderly patients (23).

Seventy patients were treated by this protocol. The CR rate of 79% and the overall response rate of 97%, were rates comparable with those of other studies. Ten out of 13 PR cases had stage IV disease and PR was not achieved in two patients with stage IVB disease. Fujii et al. reported similar response.

Figure 1. Overall survival and local control rate in all cases.

Table IV. Trial results of altered fractionated radiotherapy with concurrent chemotherapy.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. patients</th>
<th>RT schedule (Gy)</th>
<th>CCT</th>
<th>2-Year LCR(%)</th>
<th>2-Year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duke Univ., 1998 (9)</td>
<td>116</td>
<td>HF (70)</td>
<td>CDDP/5-FU</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>Univ. Munich, 1998 (10)</td>
<td>130</td>
<td>AF (70.2)</td>
<td>CDDP/5-FU/LV</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Yugoslavia, 2000 (11)</td>
<td>130</td>
<td>HF (77)</td>
<td>CDDP</td>
<td>60</td>
<td>68</td>
</tr>
<tr>
<td>Univ. Vienna, 2000 (12)</td>
<td>80</td>
<td>AF (55.3)</td>
<td>MMC</td>
<td>48*</td>
<td>50</td>
</tr>
<tr>
<td>RCCTG, 2005 (13)</td>
<td>190</td>
<td>HAF (70.6)</td>
<td>5-FU/MMC</td>
<td>58</td>
<td>50</td>
</tr>
<tr>
<td>FNCLCC- GORTEC, 2006 (14)</td>
<td>163</td>
<td>HF (75.6-80.4)</td>
<td>CDDP/5-FU</td>
<td>59</td>
<td>38</td>
</tr>
<tr>
<td>RTOG 99-14, 2008 (15)</td>
<td>76</td>
<td>HAF (72)</td>
<td>CDDP</td>
<td>67</td>
<td>70</td>
</tr>
<tr>
<td>Univ. Leuven, 2009 (16)</td>
<td>90</td>
<td>HAF (72)</td>
<td>CDDP</td>
<td>70</td>
<td>74</td>
</tr>
<tr>
<td>SAKK 10/94, 2012 (17)</td>
<td>112</td>
<td>HF (74.4)</td>
<td>CDDP</td>
<td>55</td>
<td>59</td>
</tr>
<tr>
<td>Present study, 2012</td>
<td>70</td>
<td>HF (72)</td>
<td>DTX</td>
<td>73</td>
<td>70</td>
</tr>
</tbody>
</table>

RT, Radiotherapy; CCT, concurrent chemotherapy; LRC, local control rate; OS, overall survival; HT, hyperfractionation; AF, accelerated fractionation; HAF, hyperfractionated accelerated radiotherapy; CDDP, cisplatinum; 5-FU, 5-fluorouracil; LV, leucovorin; MMC, mitomycin C; DTX, docetaxel; RCCTG, Radiotherapy Cooperative Clinical Trials Group of the German Cancer Society; FNCLCC, Federation Nationale des Centres de Lutte Contre le Cancer; GORTEC, Groupe Oncologie Radiotherapie Tete et Cou; RTOG, Radiotherapy Oncology Group; SAKK, Swiss Association for Clinical Cancer Research. *Crude control rate of 38/80.
and CR rates of 96.9% and 50%, respectively, using 60 Gy/30 fractions of conventional radiotherapy with 10 mg/m² of weekly docetaxel for advanced HNSCC (24). Relapse or recurrence developed in 43% (30 patients) in this study. Infield recurrence was observed in 19 patients, three of whom were successfully salvaged by surgery and two of whom by radiotherapy. The other 14 could not be salvaged even by multimodal treatment. More infield recurrences (19 patients) were observed than distant metastases (12 patients). Additional boost-dose to primary and pathological lymph nodes must be considered if possible.

LCR and OS were slightly higher than that of other studies, possibly because of the number of patients with stage II HNSCC in this study. Comparison of OS and cause CSS rates between clinical stages revealed that outcomes in patients with stage II and III disease were relatively favorable, but mortality was almost 50% in those with stage IVA disease, and all patients with stage IVB disease had died within 3 years of treatment. Comparing the results by site, hypopharyngeal cancer was associated with the most unfavorable outcomes (Table III). The treatment protocol described in this study could not lead to improvement of outcomes in stage IVB or hypopharyngeal cancer.

As for acute toxicity, levels of hematological toxicity were mild and acceptable. But non-hematological adverse effects, mucositis and pain were a problem. Grade 3 mucositis was observed in 61% and mucositis above grade 2 were observed in 96% (67 patients). We treated mucositis by anti-inflammatory agent, mucoprotective agent, anti-ulcerogenic drug and nutrition support. Weekly administration of concurrent docetaxel was discontinued until pain was tolerable and soft solid food intake resumed (n=21, 30%). Mucositis was a dose-limiting toxicity in this protocol. Dermatitis of grade 2 (n=38) and 3 (n=2) were observed, but were manageable by skin care and did not necessitate interrupting the treatment.

Regarding late toxicity cases, xerostomia of grade 3 (n=4) and 2 (n=25) was observed. More conformal radiotherapy, such as parotid gland-sparing IMRT, could improve salivary dysfunction.

Concomitant chemotherapy with irradiation improves outcomes, although it also enhances some toxicities. Our previous study of conventional fractionated radiotherapy with concurrent docetaxel and carboplatin for advanced HNSCC reported 69% of grade 3 mucositis (18) and another of our previous studies of neo-adjuvant chemotherapy followed by HFRT with concurrent carboplatin resulted in 38% of grade 3 mucositis (8). The present study with docetaxel combination therapy demonstrated equivalent efficacy to that of platinum-based concurrent chemotherapy, but increasing mucosal toxicity was the dose-limiting toxicity. These normal tissue toxicities could be reduced using more conformal irradiation techniques such as IMRT or particle beam therapy (25-27).

In conclusion, this study demonstrated that HFRT with weekly docetaxel is a regimen comparable in efficacy to HFRT with cisplatin. Combination with a more conformal radiotherapy technique and a great boost-dose to the primary site and pathological lymph nodes, adding to this protocol may reduce the incidence of mucositis and xerostomia and improve local control and survival.

References


Received May 18, 2012
Revised July 23, 2012
Accepted July 24, 2012