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Original research

Feasibility of postoperative concurrent chemoradiotherapy in Japanese patients with oral squamous cell carcinoma showing high-risk factors for recurrence

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ABSTRACT

Concurrent chemoradiotherapy with high-dose single-agent cisplatin has been recognized worldwide as the standard treatment for resectable advanced head and neck squamous cell carcinoma with a high risk of recurrence. However, because of severe acute adverse events compared with radiation therapy alone, this regimen is still not widely used in Japan. Hence, we evaluated the feasibility and safety of this regimen in Japanese patients with oral squamous cell carcinoma having high risk factors for recurrence. Microscopically incomplete resection, extracapsular extension, and two or more lymph node metastases were defined as the high-risk factors. The treatment regimen included three cycles of cisplatin at a dose of 100 mg/m^2 and concomitant radiation therapy (66 Gy/33 Fr). Nineteen patients were enrolled. The completion rate with a cumulative cisplatin dose of more than 200 mg/m^2 was 78.9%, and 63.1% with a cumulative cisplatin dose of more than 240 mg/m^2. With an average follow-up period for survivors of 15.8 months (range 3–46 months), 24-months LRC, RFS, and OS were 93.8%, 62.2%, and 79.1%, respectively. This cisplatin and concurrent radiation regimen is feasible for Japanese patients with oral squamous cell carcinoma having high-risk factors for postoperative recurrence.

1. Introduction

Oral squamous cell carcinoma (OSCC) has been reported to account for nearly 3% of all cancers globally [1,2]. The majority of patients with head and neck squamous cell carcinoma (HNSCC) present with locally or regionally advanced disease [3,4]. Various strategies have been proposed to improve the outcome among patients having resectable, locally advanced HNSCC with high-risk factors for recurrence or metastasis. Surgery is the most established mode of initial definitive treatment for the majority of OSCC [5–7]. In most institutions, primary surgery of locally advanced HNSCC was generally followed by postoperative radiotherapy. However, it was reported that the rates of loco-regional recurrence, distant metastasis, and 5-year survival rate were 30%, 25%, and 40%, respectively [8]. In resectable advanced OSCC, the improvement of strategies for control of loco-regional recurrence and distant metastasis should lead to a good outcome of OSCC treatment.

In 2004, the European Organization for Research and Treatment of Cancer (EORTG) and the Radiation Therapy Oncology Group (RTOG) reported the results of two randomized trials (EORTG trial #22931 and RTOG trial #9501) that evaluated the role of concomitant chemotherapy-enhanced radiation therapy in the postoperative setting for HNSCC patients with a high risk of recurrence and metastasis [9,10]. Both trials compared the addition of concomitant relatively high doses of cisplatin (on days 1, 22, and 43) to radiotherapy versus radiotherapy alone applied after surgery in patients with HNSCC at high risk of recurrence [9,10]. The RTOG #9501 trial demonstrated significant improvements of

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loco-regional control and disease-free survival, but not overall survival [10]. Similarly, the EORTG trial #22931 demonstrated significant improvements of loco-regional control, disease-free survival, and overall survival [9]. Recently, concurrent chemoradiotherapy with high-dose single-agent cisplatin has been recognized worldwide as the standard treatment for resectable, advanced HNSCC with a high risk. However, a retrospective study on three Japanese patients with nasopharyngeal cancer receiving cisplatin and concurrent radiotherapy reported severe acute toxicities [11]. As a result, this regimen is still not widely used in Japan.

The purpose of this study is to evaluate the feasibility of this regimen in Japanese advanced OSCC patients at high risk. This investigation may be helpful for the management of advanced OSCC patients postoperatively.

2. Patients and methods

2.1. Patients

In this study, the entry criteria were as follows: (1) OSCC confirmed pathologically; (2) completely resected disease macroscopically; (3) high-risk characteristics (any or all of the following: histologic evidence of invasion of two or more regional lymph nodes, extracapsular extension of nodal disease, and microscopically involved margins of resection); (4) patient age at or under 75 years; (5) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 or less; (6) adequate organ functions; (7) no active concomitant malignant tumor; (8) no prior chemotherapy or radiotherapy; and (9) a white blood-cell counts at least 3500 per cubic millimeter, a platelet count of at least 100,000 per cubic millimeter, a hemoglobin concentration of at least 11.0 g per deciliter, and a serum creatinine concentration of 1.36 mg per deciliter. The study protocol was approved by the institutional review committee of each institute. All patients gave written informed consent in accordance with institutional guidelines. This study performed in the consecutive study series of the patients of each institutes from April 2008 to March 2013.

2.2. Treatment methods

Concomitant radiation therapy at 4–6 MV was administered at 2 Gy/day on 5 days/week. A large volume encompassing the primary site and all draining lymph nodes at risk received a dose of up to 60 Gy in 30 fractions. Regions that were at high risk for malignant dissemination or that had inadequate resection margins received a 6 Gy boost (a total of 66 Gy in 33 fractions). The dose to spinal code was limited to 46 Gy. Chemotherapy consisted of 100 mg of cisplatin per square meter of body surface area on days 1, 22, and 43 of the course of radiotherapy. Patients received prophylactic hydration and antiemetic agents. Aprepitant was approved in Japan in October 2009, and therefore not available during the study period before October 2009. Therefore, we used a 5-HT3 antagonist and dexamethasone 16–20 mg on Day 1 and dexamethasone 8–16 mg on Day 2–3. After the approval of aprepitant, we used the dexamethasone 13.6 mg, 5-HT3 antagonist, and aprepitant on Day 1 and dexamethasone 6.6 mg and aprepitant on Day 2–4. We used the oral administration of cepharanthin, adenin, and pilocarpine during the radiation therapy. Cisplatin was postponed if the absolute neutrophil count fell below 1000/mm^3 or platelet count fell below 75,000/mm^3. Cisplatin dose was decreased to 80 mg/m^2, if creatinine clearance dropped to 50–60 ml/min. Cisplatin dose was also decreased with Grade 3 hematological toxicity from 100 mg/m^2 to 80 mg/m^2. Patients were evaluated every month, and examined with enhanced computed tomography scan and ultrasonography every 3 months for the first 12 months.

Table 1
Patient characteristics (n = 19).

	Number of patients
Age: average (range)	60.9 (37–73)
Gender: female/male	4/15
PS: 0/1	14/5
Primary site	
Tongue	11
Lower gingiva	3
Oral floor	2
Buccal mucosa	2
Upper gingiva	1
Stage	
II	1
III	6
IV	11
Locoregional recurrent disease	1
High-risk factors	
MLM + ECE	12
ICR + MLM + ECE	3
ECE	2
ICR + ECE	1
MLM	1
Histology: squamous cell carcinoma	
Well differentiated	8
Moderately differentiated	6
Poorly differentiated	5

2.3. Study design

The primary endpoint was treatment compliance. Complete treatment delivery was defined as administration of more than 60 Gy radiotherapy dose and more than 200 mg/m^2 or 240 mg/m^2 CDDP administration no later than 14 days after the end of irradiation. Secondary endpoints were overall survival (OS), relapse-free survival (RFS), loco-regional control (LRC), and adverse events. OS was defined as the time from initiation of chemoradiotherapy to death from any cause, and RFS as the time from initiation of chemoradiotherapy to the occurrence of recurrence or death from any cause. The duration of LRC was defined as the time from initiation of chemoradiotherapy to the occurrence of loco-regional recurrence. Survival curves were produced by the Kaplan–Meier method.

2.4. Toxicity evaluation

Toxicities were graded using the Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4.0). The treatment-related adverse effects were categorized as acute (occurring within 90 days of initiation of chemoradiotherapy) or late (continuing or occurring after 90 days).

3. Results

3.1. Patient characteristics

In this study, nineteen patients were enrolled, and their characteristics are summarized in Table 1. In terms of age, the 15 male and 4 female patients ranged from 37 to 73 years old, with an average of 60.9 years old. Eleven patients had primary sites in the tongue, three in the lower gingiva, and two in each of the oral floor and buccal mucosa, and one in the upper gingiva. Eighteen patients had locally advanced disease and one had loco-regional recurrent disease. All patients underwent definitive surgery with curative intent. In terms of the pathological stage, 11 patients were classified as having Stage IV disease, 6 as having Stage III, and 1 as having Stage II. Regarding the high-risk features, 12 patients had multiple lymph node metastasis (two or more lymph nodes: MLM) and extracapsular extension (ECE), 3 had microscopically involved