Jpn J Clin Oncol 2005;35(4)173–176
doi:10.1093/jjco/hyi058

Original Articles

Phase I Trial of Weekly Docetaxel and Concurrent Radiotherapy for Head and Neck Cancer in Elderly Patients or Patients with Complications

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Received December 10, 2004; accepted February 14, 2005

Objective: We planned a phase I study of radiotherapy combined with weekly docetaxel for elderly patients or patients with complications to find out the optimal dose.
Methods: Five consecutive weekly administrations of docetaxel were accompanied by radiotherapy for patients diagnosed with squamous cell carcinoma of the head and neck. The starting dose of docetaxel was 10 mg/m^2 with escalation at 2 mg/m^2 per step.
Results: Fifteen patients were enrolled in this trial. The maximal tolerated dose was 14 mg/m^2, so the recommended dose was determined as 12 mg/m^2. Hematological toxicity was sufficiently weak. Common dose-limiting toxicity was stomatitis within the radiation field.
Conclusions: This protocol was thought to be practical for elderly patients or those with medical complications.

Key words: elderly patients – concurrent – docetaxel – head and neck – radiotherapy

INTRODUCTION

Radiation therapy plays a significant role in advanced head and neck squamous cell carcinoma (SCCHN), although locoregional failure remains the major cause of treatment failure. Meta-analysis provided level I evidence of survival benefits under concurrent chemoradiotherapy (1), thus it is thought to be a standard treatment for patients without medical complications. Platinum-based agents are now widely used, although their toxicities, especially for renal and gastrointestinal complications, limit treatment benefits for elderly patients or those with additional medical illnesses.

Docetaxel is one of the most active agents for SCCHN (2) and is believed to be a radiosensitizer (3). Docetaxel promotes the polymerization and stabilization of microtubules, leading to an accumulation of cells at the G_2/M boundary, relatively the most radiosensitive phase of the cell cycle. In the initial development, docetaxel was administered once every 3 weeks; however, weekly administration now appears to offer several advantages in terms of toxicity, especially for myelosuppression (4). In addition, weekly administration would increase the chance of enhancement of the effects of radiation therapy. In this setting, hospitalization and treatment costs could be reduced, therefore those groups of patients would have a chance of chemoradiotherapy (5). We thus planned a phase I study to evaluate its clinical practicality.

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PATIENTS AND METHODS

ELIGIBILITY

Patients with histologically confirmed SCCHN were enrolled in a phase I trial of combined radiotherapy and weekly docetaxel. Written informed consent was obtained from each patient before enrollment. Patients had either previously untreated SCCHN or had been previously treated with radiotherapy and/or chemotherapy (excluding from docetaxel) with a minimum of 1 month since the last treatment. Specific eligibility criteria were as follows: (i) patients were required to be aged ⩾70 years; younger patients were eligible only if they were considered to be poor candidates for combination chemoradiotherapy regimens due to co-existent medical illness and/or poor performance status; (ii) an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (iii) no pulmonary or cardiovascular contraindications; (iv) adequate hematological function (WBCs ⩾4000/μl, neutrophil count ⩾2000/μl, platelet count ⩾100 000/μl and hemoglobin level ⩾11 g/dl); (v) adequate hepatic function (aspartate

aminotransferase and alanine aminotransferase <3 times normal values and total bilirubin <1.5 times normal values); (vi) adequate renal function (creatinine serum concentration <1.5 times normal values); and (vii) life expectancy >3 months.

Docetaxel

Docetaxel was administered weekly for five consecutive weeks as a 1 h intravenous infusion. Starting dose was 10 mg/m^2. Concurrent treatment with antiemetics, antibiotics, sedatives, steroids, hematopoietic growth factors and gastric protectors was permitted. An additional increase by 2 mg/m^2 up to the maximum tolerated dose (MTD) was permitted. At least three patients were treated at each dose level. Dose-limiting toxicity (DLT) was defined as grade 3 of National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2 in hematological or non-hematological toxicities, excluding mucosa, skin, nausea and vomiting. Grade 4 of these latter non-hematological toxicities was defined as the DLT. When the DLT appeared, three patients were added into the same dose level. End-points to close the study were DLT in hematological or non-hematological toxicity if observed in two of three or three of six patients at the same dose levels. The previous dose level before the MTD was considered as the recommended dose.

Radiotherapy

For previously untreated patients, radiotherapy was administered 5 days per week in fractions of 2 Gy to the primary tumor site and involved cervical lymph nodes. At first a dose of 40 Gy to the cervical lymph node was administered for prophylaxis. In the case with glottic larynx, the primary radiation field was limited to the laryngeal box without prophylactic radiation portals. Radiation was prescribed using lateral opposing portals of 60 cobalt or a 6 MV photon. Using the cone-down technique, the radiation field was shrunk to the primary tumor site and/or involved lymph node with an adequate margin. To spare an excess dose of 45 Gy to the spinal cord, adequate radiation techniques including the conformal dynamic-rotation method were used appropriately. The total dose to the primary tumor site was planned to be 60–66 Gy, and 66–70 Gy for any involved cervical lymph node.

For previously radiated patients, radiotherapy was given with a daily 1.8 Gy fraction. The total dose to the primary lesion was minimized to 39.6 Gy, so that the sum of radiation doses in both initial and re-treatments did not exceed 100 Gy. The spinal cord was never irradiated above 45 Gy in all cases. In these cases, radiation fields were planned to cover only the clinical tumor target.

Treatment breaks were allowed for confluent mucositis, dyspnea due to laryngeal edema, and grade 3 or more of unexpected non-hematological toxicity. Surgery of the primary site was recommended for operable patients with resectable disease who failed to achieve at least a partical response after 40 Gy. Neck dissection was permitted in patients who failed to achieve clinical complete response of the neck at the end of treatment. Any additional therapy was permitted after this protocol, if indicated.

Evaluation and Follow-up

After the completion of therapy, patients were evaluated by physical and fiberscopic examination at monthly intervals for the first year, and every other month for the second year. Computed tomography (CT) scans and/or magnetic resonance imaging (MRI) were performed at 6 and 12 months, and annually thereafter. Complete response was defined as the disappearance of all clinically evident tumors and no new disease. A partial response was defined as a >50% reduction of the sum of the products of perpendicular tumor measurements and no new disease. Stable disease was defined as less than a partial response and a <25% increase in all dimensions of measurable disease, and progressive disease was defined as a >25% increase or new sites of disease. Overall survival was assessed using the Kaplan–Meier method starting from the date of treatment initiation.

RESULTS

Characteristics of the Patients

Fifteen patients (10 males and five females) with a median age of 74 years were enrolled in this study. Four patients were enrolled in this protocol because of medical illness (two uncontrollable diabetes, two unstable angina), and 11 patients (73.3%) because they were elderly. Five patients were treated with chemoradiotherapy before this protocol. One patient was diagnosed with recurrence after radical surgery for tongue cancer at enrollment. Table 1 gives details of patient and tumor characteristics.

Dose-limiting Toxicity

Table 2 shows the hematological toxicities observed at each dose level. Hematological toxicities were minimal in all cohorts, reflecting the reduced capability for cytotoxic agents among these patients. No patient experienced grade 3 or higher hematological toxicity. DLTs did not occur in any dose group.

Table 3 shows the non-hematological toxicities observed by dose level. The most significant toxicity was stomatitis within the radiation fields. Of the 15 patients, six developed grade 3 mucositis, and three suffered grade 4 mucositis (all were grouped at dose level III). None of the patients in level I and II groups experienced treatment interruption due to DLTs.

DISCUSSION

Docetaxel is one of the active agents for head and neck malignancy (6–8). It had been used in multi-agent chemotherapy by induction setting. In three phase II studies of docetaxel-based regimens of induction therapy for patients with locally advanced SCCHN, the overall response rates range from 93 to 100%, with complete response rates of 40–63%. The

Table 1. Patient characteristics

No. of patients enrolled	15
Sex	
Male	10
Female	5
Age (years)	61–87 (median 74)
Performance status (ECOG)	
1	10
2	5
Prior therapy	
None	9
Operation	1
Chemoradiotherapy	5
Primary tumor location	
Larynx	6
Tongue/oral cavity	3
Nasopharynx	1
Oropharynx	4
Hypopharynx	1
Stage	
I–II	5
III	1
IV	4
Recurrence	5

Table 2. Hematological toxicity

Level	I (10 mg/m^2)				II (12 mg/m^2)				III (14 mg/m^2)			
Grade	1	2	3	4	1	2	3	4	1	2	3	4
Hemoglobin	1	1	0	0	4	2	0	0	3	2	0	0
Leukocytes	2	0	0	0	2	1	0	0	1	1	0	0
Neutrophils	0	0	0	0	1	0	0	0	1	1	0	0
Platelets	1	0	0	0	4	2	0	0	3	2	0	0

Table 3. Non-hematological toxicity

Level	I (10 mg/m^2)				II (12 mg/m^2)				III (14 mg/m^2)			
Grade	1	2	3	4	1	2	3	4	1	2	3	4
Stomatitis	0	2	1	0	0	2	4	0	0	2	1	3
Dermatitis	0	3	0	0	2	3	1	0	2	3	0	1
Liver	2	0	0	0	1	2	0	0	1	2	0	0
Kidney	0	0	0	0	1	0	0	0	2	0	0	0
Anorexia	1	1	0	0	0	0	2	0	0	2	2	0
Edema	0	1	0	0	0	0	0	0	0	0	0	0

primary toxicities were neutropenia and febrile neutropenia (8). Although it was an effective method, these regimens were not planned with concurrent chemoradiotherapy due to acute toxicity. Recently it was noted that neutropenia could be remarkably reduced by weekly administration (4,5). Therefore, this method was used with concurrent chemoradiotherapy (9–11), and was thought to be theoretically effective (1). Using weekly administration, the hematological toxicity became sufficiently weak and treatment could be easily planned in an out-patient setting, so we tried to apply this protocol to the elderly and/or patients with another medical illness who were not thought to be candidates for intensive systemic chemotherapy with platinum agents.

In our prospective phase I study, we experienced sufficiently mild hematological toxicity, even though our cohort consisted of patients with several clinical limitations. No patient developed grade 3 or more hematological toxicity. Two of 15 patients developed grade 2 leukopenia, and only one of the 15 developed grade 2 neutropenia. However, the most common toxicity was stomatitis within the radiation field. Nine of 15 patients experienced radiation stomatitis due to chemoradiotherapy. This is quite similar to other reported data (9–11). Calais et al. (9) reported the results of a phase II study including 70 Gy/35 fx of radiotherapy with 20 mg/m^2 of weekly docetaxel for stage III/IV oropharyngeal carcinoma. The rate of grade 3 and 4 mucositis was 84%. Suzuki et al. (10) reported a phase I study of 60–70 Gy/30–35 fx with concurrent weekly docetaxel. The DLT was mucositis (one of 12 for grade IV, one for prolonged grade III). They reported a recommended dose of docetaxel of 15 mg/m^2. Karasawa et al. (11) reported clinical results of concurrent chemoradiotherapy using weekly docetaxel combined with daily carboplatin administration. Altered fractionation was included in reported patients. They reported grade 3 mucositis in 69% of patients and grade 2 dermatitis in 56% of patients. However, these reported data were from patients without a medical limitation. Therefore, we believe our treatment protocol is quite meaningful in clinical practice especially for clinically handicapped groups.

We were encouraged by our phase I data showing adequate low toxicity and high treatment completion rate, so we will advance to a phase II trial. Considering the clinical background of the targeted group, more careful attention should be paid to the feasibility of this protocol. Therefore, we intend to limit the study to patients diagnosed with SCCHN of the larynx or hypopharynx with stage II–III disease, because these cases could have a minimized radiation field size with an endurable compromise in treatment outcomes (12). Smaller radiation fields would lead to a lower toxicity of concurrent chemoradiotherapy with weekly docetaxel. In addition, there would be an increased chance of larynx preservation by concurrent chemoradiation with weekly docetaxel, providing benefit to the patients' quality of life. The primary end-point of this phase II study is larynx preservation for elderly patients or patients with complications. This prospective multicenter phase II study will be supported by a Grant-in-Aid for Cancer Research (Grant Nos 14-15 and 16-12) from the Ministry of Health, Labor and Welfare in

Japan, the Japan Society for the Promotion of Sciences (JSPS), and Japanese Foundation of Aging & Health (JFAH).

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