Concomitant Weekly Cisplatin and Radiotherapy for Head and Neck Cancer

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Objective: The most common chemoradiotherapy regimen is high-dose (100 mg/m2) three-weekly cisplatin with concomitant radiotherapy; however, this protocol is associated with acute and late toxicities. Here, we reviewed the dose intensity and toxicity for concomitant weekly cisplatin and radiotherapy in patients with head and neck cancer.

Methods: Fifty-three patients with untreated head and neck cancer were enrolled and evaluated at our institution from April 2006 to April 2010. Weekly cisplatin (40 mg/m2) was given on weeks 1, 2, 3, 5, 6 and 7 with radiotherapy, which comprised a standard dose of 70 Gy delivered in 35 daily fractions over 7 weeks.

Results: Fifty-one patients (96.2%) received the full dose of radiotherapy, while the course was disrupted by adverse events in two. Over the course of the chemotherapy, 31 patients (58.5%) received more than 200 mg/m2 cisplatin. The toxicity was manageable in all except one patient, who died of sepsis after completing treatment. The 2-year overall survival rate and local progression-free rate for all patients were 93.7% and 88.0%, respectively. The primary site showed a complete response in 52 patients (98.1%) and a partial response in 1 patient (1.9%). The primary disease was well controlled by chemoradiotherapy in 47 patients (88.7%).

Conclusions: Weekly cisplatin could be easier to manage than three-weekly cisplatin, because patients can be monitored more regularly for toxicity allowing the schedule to be altered if required. This regimen appears to be a suitable alternative to three-weekly high-dose cisplatin with concomitant radiotherapy.

Key words: chemotherapy – cisplatin – radiotherapy – chemoradiotherapy

INTRODUCTION

Locoregionally advanced head and neck cancer (HNC) is generally treated with surgery followed by postoperative radiotherapy (RT). However, definitive concomitant chemoradiotherapy (CRT) is an alternative treatment option (1). Cisplatin is the most common agent used in combination with RT, and is one of the best studied. The standard regimen is three-weekly high-dose (100 mg/m2) cisplatin (three cycles) concurrent with RT (2,3).

However, cisplatin at a dose of 100 mg/m2 with concomitant RT is associated with significant acute and late toxicities (2,4,5). Furthermore, the completion rate for this regimen is relatively poor (2,3). The use of a lower cumulative cisplatin dose or a more fractionated cisplatin dose has therefore been suggested (6–8).

Renal function has been reported to decrease rapidly with aging in the Japanese population, although the underlying reason remains unclear (9). The recommended dose of cisplatin is 60–70 mg/m2 for patients with HNC according to...
the Japanese Ministry of Health, Labor and Welfare. A retrospective study of three Japanese patients with nasopharyngeal cancer receiving cisplatin and concurrent RT reported severe acute toxicities (10). By contrast, weekly cisplatin at a dose of 40 mg/m² was found to be well tolerated and to have acceptable toxicity, despite the large RT fields employed, for the treatment of nasopharyngeal carcinoma (11).

Weekly cisplatin at a dose of 40 mg/m² has been the standard schedule for HNC at our institution since 2006. In the present study, we calculated the dose intensity and evaluated the toxicity of this regimen in patients with HNC at our institution retrospectively.

PATIENTS AND METHODS

Patients

To be eligible for inclusion in this study, patients were required to have histologically proven Stage II–IV carcinoma of the oropharynx, hypopharynx or larynx. All patients were 75 years of age or younger, and had not received previous treatment for the tumor except neck dissection. Patients were required to be free of other active cancers, as well as distant metastases, and to meet the following criteria: a World Health Organization performance status of 0–2; a white-cell count of at least 4000/mm³; a platelet count of at least 1 00 000/mm³; a hemoglobin concentration of at least 9.5 g/dl; serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase levels of less than twice the upper limit of the normal range; a total bilirubin concentration of <2.0 mg/dl; a serum creatinine concentration of <1.5 g/dl; a blood urea nitrogen concentration of <25 mg/dl; and a creatinine clearance of more than 60 ml/min. The disease had to be measurable or amenable to evaluation, and had to be documented as precisely as possible before treatment by endoscopy, including computed tomography (CT) and/or magnetic resonance imaging (MRI). All patients were initially evaluated by a multidisciplinary team consisting of otolaryngologists and radiation oncologists, and the tumors were classified according to the 2002 Union Internationale Contre le Cancer (UICC) staging system. Written informed consent was obtained from all patients before entry into the study. Patients who were pregnant or breast-feeding were excluded from the study.

Chemotherapy

Weekly cisplatin was administered at a dose of 40 mg/m² on weeks 1, 2, 3, 5, 6 and 7 of the RT. Patients received prophylactic hydration (4 l) and 5HT₃ antagonists plus dexamethasone for anti-emetic prophylaxis. The intended maximum total dose of cisplatin was 240 mg/m². The cisplatin dose was modified on a case-by-case basis according to the level of leucopenia and/or thrombocytopenia, the serum creatinine and/or creatinine clearance, the presence of liver dysfunction and/or infectious disease, and the patient’s wishes. In addition, weekly cisplatin was altered to weekly carboplatin [area under the curve (AUC) = 1.5] in some cases based on the toxicity.

Preparation for percutaneous endoscopic gastrostomy feeding before treatment was recommended. The use of non-steroidal anti-inflammatory drugs was avoided, in order to prevent any synergistic toxic effects with cisplatin on renal function.

Radiotherapy

A standard dose of 70 Gy was delivered in 35 daily fractions over 7 weeks to all of the patients. All of the patients received external RT (40 Gy/20 fractions/4 weeks), in the form of 4 or 6 MV photons produced by a linear accelerator, to the primary sites and regional lymphatic area. The treatment was planned using a CT simulator and a three-dimensional dose-calculation computer. For patients who were suspected of having lymph-node metastases, the lower-neck region and supraclavicular fossa were prophylactically irradiated with a total of 40 Gy using an anterior single port. Electron beams were used to boost the dose delivered to the posterior cervical lymph nodes. The dose delivered to the spinal cord was kept below 40 Gy in all instances. After the initial dose of 40 Gy had been administered, an additional dose of 30 Gy was given with a shrunken field in 15 fractions over 3 weeks.

Evaluation of Toxicity and Response

Toxicities were graded using the Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0. For measurable lesions, responses were evaluated by clinical examination and/or CT or MRI studies 6–8 weeks after the completion of therapy using the Response Evaluation Criteria in Solid Tumors (RECIST). CT and MRI were performed 6–10 weeks after the end of RT as a convenient means of determining target-lesion progress and identifying emerging new lesions.

Positron-emission tomography (PET) and PET-CT were used to support the diagnosis. Based on the radiographic changes related to treatment, it can be difficult to distinguish between the scar tissue and residual tumor tissue. Over time, however, the scar tissue will remain stable, whereas the remaining tumor tissue can progress. We designed the patient outcomes to reflect this uncertainty: a patient with radiological changes that remained stable over time, and no signs or symptoms of disease, was considered to be ‘progression free’. Biopsy was performed only to document recurrence when indicated.

Statistical Considerations

Data on the disease site, Tumor-Node-Metastasis (TNM) stage, RT dose/fractionation and chemotherapy regimen were
collected. Incidences of delays to therapy, acute toxicity, dose reduction and missed treatments for both chemotherapy and RT were also recorded.

The primary endpoint was treatment compliance. Complete treatment delivery was defined as the administration of the 70 Gy RT dose within 63 days, and the completion of five or six courses of cisplatin. Treatment compliance was evaluated based on the rate of complete treatment delivery.

Cases of persistent or recurrent primary disease after the completion of CRT were considered to be local failures unless salvage was successful. The probabilities of overall survival, which included death from any cause, and the local control rates (the local progression-free rates computed from the beginning of treatment until the time of local relapse) were calculated by the Kaplan–Meier method.

RESULTS

PATIENT CHARACTERISTICS

Fifty-three patients (49 males and 4 females) were enrolled in the study and were evaluated from April 2006 to April 2010 (Table 1). The patients ranged in age from 40 to 75 years (median = 62 years). The most common site of the primary disease was the hypopharynx (22 patients), followed by the oropharynx (18 patients), larynx (12 patients) and oral cavity (1 patient). Two patients underwent bilateral neck dissection prior to CRT. One patient with T2N2b laryngeal cancer and synchronous esophageal cancer underwent esophagectomy and bilateral neck dissection prior to CRT in order to preserve the larynx. One patient with unknown primary bilateral neck cancer underwent bilateral neck dissection and panendoscopy with biopsies of the pharynx. A pathological examination revealed the base of the tongue as the primary site in this case, and the patient subsequently underwent CRT.

The clinical stages are listed in Table 2. In total, 30 patients had Stage IV disease, 6 had Stage III disease and the remaining 17 had Stage II disease.

All of the patients were closely observed during follow-up. The follow-up period of survivors ranged from 7 to 57 months (median = 29 months; mean = 29 months).

ADVERSE EVENTS

The acute adverse events observed, including hematological and non-hematological toxicities, are summarized in Table 3. One patient died of sepsis after completing the treatment; this patient exhibited Grade 3 leukopenia, anemia, fever and renal dysfunction, and Grade 4 thrombocytopenia, liver dysfunction and hypernatremia. Grade 4 hematological toxicities were not observed among the other patients. Grade 3–4 mucositis was observed in 21 patients (39.6%). Mild-to-intermediate renal dysfunction was observed in 15 cases: Grade 1 creatinine was present in 13 patients (24%), Grade 2 in 1 (2%) and Grade 3 in 1 (2%). The other Grade 3–4 non-hematological side effects observed included nausea/vomiting (n = 3), liver dysfunction (n = 3), dermatitis (n = 18), fever (n = 4), hyponatremia (n = 1), hypernatremia (n = 1), appetite (n = 8) and hyperglycemia (n = 1). None of the surviving patients showed evidence of disease, and all except one were able to achieve oral intake without feeding-tube support. Pharyngeal stenosis occurred in one patient with T3N1 hypopharyngeal cancer, who suffered from repeated pneumonia and underwent a total laryngopharyngectomy and free-jejunum transfer. One patient experienced osteonecrosis of the mandible, but did not require surgical treatment.

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<th>Table 1. Clinical characteristics (n = 53)</th>
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Grade 2 in 1 (2%) and Grade 3 in 1 (2%). The other Grade 3–4 non-hematological side effects observed included nausea/vomiting (n = 3), liver dysfunction (n = 3), dermatitis (n = 18), fever (n = 4), hyponatremia (n = 1), hypernatremia (n = 1), appetite (n = 8) and hyperglycemia (n = 1). None of the surviving patients showed evidence of disease, and all except one were able to achieve oral intake without feeding-tube support. Pharyngeal stenosis occurred in one patient with T3N1 hypopharyngeal cancer, who suffered from repeated pneumonia and underwent a total laryngopharyngectomy and free-jejunum transfer. One patient experienced osteonecrosis of the mandible, but did not require surgical treatment.
**TOTAL TREATMENT COMPLIANCE**

In total, 51 of the patients (96.2%) received the full dose of RT (70 Gy) over a median period of 50 days (range = 46–62 days). The radiation course was disrupted in two of the patients by adverse events. The reasons for extension of the RT course beyond 50 days were holidays and machine maintenance, except in two patients. A total of 34 patients (64.2%) completed five (15 patients) or six (19 patients) courses of the chemotherapy; 11/17 (64.7%) with Stage II and 23/36 (63.9%) with Stage III/IV. However, in three of these patients, the dose of cisplatin was modified due to adverse effects. As a result, 31 patients (58.5%) received more than 200 mg/m² of cisplatin. The cisplatin treatment was stopped in 2 patients (3.8%) after one course, in 3 patients (5.7%) after two courses, in 4 patients (7.5%) after three courses and in 10 patients (18.9%) after four courses. Four of the five patients who received only one or two courses of cisplatin were switched to weekly carboplatin (AUC = 1.5). Finally, the average total amount of cisplatin administered was 185 mg/m² (median = 190 mg/m²) when data from all patients were included in the analysis, and the average dose intensity of cisplatin was 26.5 mg/m²/week.

**OVERALL SURVIVAL AND LOCAL CONTROL**

The 2-year overall survival and local progression-free rates for all patients were 93.7% and 88.0%, respectively (Fig. 1).

**RESPONSE OF THE PRIMARY DISEASE**

Of the 53 patients who entered into the treatment program, complete responses at the primary site were observed in 52 (98.1%) and partial responses in 1 (1.9%). The primary disease was well controlled by CRT in 47 patients (88.7%). The remaining six patients (11.3%) had persistent or recurrent primary disease after completing CRT. All six of these patients underwent salvage surgery, and four subsequently survived and remained disease-free.
RESPONSE OF NECK DISEASE

Among the 33 patients with positive neck disease, two underwent neck dissection prior to CRT. Among the remaining 31 patients, the disease was well controlled by CRT without surgery in 20 patients (64.5%). Eight patients with obvious or suspected persistent neck disease after CRT were treated successfully by salvage neck dissection. In four of these patients, no viable cancer cells were observed in the surgical specimens. One patient with persistent neck disease after CRT received chemotherapy, which successfully treated the disease. Two patients underwent neck dissection when they received salvage surgery for recurrent primary disease. Both patients had no viable cancer cells in the surgical specimens, but one had recurrence in the primary and neck lesions. Thus, in 25 of the 31 patients (80.6%), the positive neck disease was well controlled by CRT. At the time of writing, 32 of the 33 patients had successfully controlled disease.

SITES OF UNCONTROLLED RECURRENCE

The site of uncontrolled recurrence was identified whenever possible. Uncontrolled recurrence initially occurred at distant metastases in four patients, at the primary site in one patient and at the primary site and regional lymph nodes in one patient. One patient died of leukemia without recurrence in the head and neck region.

DISCUSSION

Three-weekly cisplatin at a dose of 100 mg/m² concurrent with RT is considered to be the standard of care for the non-surgical treatment of advanced HNC, based on several Phase III trials (2,3). However, this protocol has been associated with significant acute and late toxicities (2,4,5). Furthermore, the completion rate of this regimen has been reported to be relatively low, with 63–85% of patients in the CRT arm completing all three of the planned cycles of concurrent chemotherapy in several clinical trials (2,3,5). Poor compliance over three cycles of high-dose cisplatin was also reported in a series of patients at the Princess Margaret Hospital in Toronto. In this retrospective study of 75 patients, 42.7% underwent all three planned cycles of chemotherapy, and only 33.3% received the intended dose without a cumulative delay of at least 7 days throughout the three cycles (12). The death rate for patients undergoing this protocol was reported to be 4−5% in Phase III trial (2,3,13), and 10% in the community setting (13).

Ho et al. (14) retrospectively compared the differences in dose intensity, delays and toxicity between weekly and three-weekly cisplatin administered concurrently with RT to patients with locally advanced HNC. The authors concluded that three-weekly cisplatin at a dose of 100 mg/m² concurrent with RT was less well tolerated than weekly cisplatin at a dose of 40 mg/m², and resulted in less patients achieving a cumulative dose of more than 200 mg/m², thereby potentially lowering the chemotherapy dose intensity. Based on these results, high-dose cisplatin might not be suitable for routine use.

The Head and Neck Intergroup conducted a Phase III randomized trial comparing radiation therapy alone with radiation and concurrent weekly cisplatin at a dose of 20 mg/m² between 1982 and 1987 (15). Although the response rate was greater in patients treated with the concurrent regimen, the median survival was only 13 months and did not differ between the two treatment arms. Although the addition of concurrent weekly cisplatin at 20 mg/m² to daily radiation did not significantly improve survival, there was some evidence of an effect. Similarly, concomitant CRT using daily low-dose (4 mg/m²) cisplatin showed disappointing results (16). A high dose of cisplatin was therefore considered necessary to achieve a good outcome (17,18).

CRT using weekly cisplatin at a dose of 40 mg/m² was found to be well tolerated in patients with advanced nasopharyngeal carcinoma in Hong Kong (11). The relatively low dose used in the investigation arm of the study resulted in no treatment-related mortalities, although this strategy could have led to suboptimal benefits. The progression-free survival rate significantly differed between the concurrent CRT arm and the RT-alone arm for patients with advanced T and N stages. Hence, after some consideration, we introduced this schedule at our institution.

The regimen appeared to be well tolerated, with low rates of severe toxicities: 62.3% of the patients completed at least five of the six planned chemotherapy cycles. A total cisplatin dose of 200 mg/m² or more was delivered to 58.5% of the patients in this study. The average dose intensity of cisplatin (26.5 mg/m²/week) was equivalent to that of three-weekly regimen (28.9 mg/m²/week) (19). With regard to toxicity, the rate of Grade 3 or greater leukopenia and mucositis in the three-weekly cisplatin regimen in patients with unresectable disease was reported to be 42.1% and 45.2%, respectively. Also in the same regimen for laryngeal preservation, the rate of Grade 3 or greater hematologic toxicity and mucositis was 47% and 43%, respectively. In the present study, the rate of Grade 3 or greater leukopenia and mucositis was 26.4% and 39.6%, respectively. Toxicity in the present study was similar or less than those in Phase III trial of three-weekly cisplatin regimen.

Weekly cisplatin could be easier to manage than three-weekly cisplatin because patients can be more regularly monitored for toxicity, and the schedule can be changed before the effects become severe, based on the patient’s condition. Because the dose delivered in each cycle is smaller, the toxicity is reduced. In the current study, five of the patients stopped receiving cisplatin after one or two courses due to the toxicity. Four of these patients subsequently received weekly carboplatin (AUC = 1.5) instead of cisplatin: creatinine clearance measured by the Cockcroft–Gault formula dropped to <50 ml/min in three patients, Grade 3 liver dysfunction was present in the fourth patient. If these patients, who were considered unsuitable for cisplatin administration, had initially
received a dose of 100 mg/m², the toxicity would have been more serious and they might have not undergone further chemotherapy or RT. We therefore consider this regimen to be a reasonable alternative to three-weekly high-dose (100 mg/m²) cisplatin concurrent with RT.

Molecular growth inhibitors such as cetuximab have recently been investigated in conjunction with radiation therapy for advanced HNC patients, and have shown promising results (20–22). The Memorial Sloan-Kettering Cancer Center reported a Phase II trial of concomitant boost RT, cisplatin (100 mg/m² in weeks 1 and 4) and cetuximab (400 mg/m² intravenously in week 1, followed by 250 mg/m² in weeks 2–10). The study was halted owing to significant adverse events, including two deaths (one from pneumonia and one from unknown causes), one case of myocardial infarction, one case of bacteremia and one case of arterial fibrillation (21). Cisplatin at a dose of 100 mg/m² concurrent with radiation therapy is an intensive regimen, and adding a molecular-targeted agent might have resulted in the unacceptable toxicity. The results of the French TREMPLIN trial indicated that only 43% of all patients receiving induction docetaxel, cisplatin, and 5-fluorouracil chemotherapy (TPF) followed by cisplatin (100 mg/m²) CRT (Arm A) were compliant with the full course of treatment, in contrast to 74% of the patients receiving induction TPF and subsequent cetuximab-containing bioradiation (Arm B) (23). Three months after treatment, there was no significant difference in laryngeal preservation between Arm A (93%) and Arm B (96%). Further clinical trials of concomitant CRT using cisplatin with a molecular-targeted agent, with or without induction chemotherapy, are required.

In conclusion, it is unlikely that cisplatin at a dose of 100 mg/m² will be an acceptable standard CRT regimen because of the severe toxicity. However, radiation therapy concomitant with cisplatin is likely to remain a key regimen. Weekly cisplatin could be easier to manage than three-weekly cisplatin, because patients can be monitored more regularly for toxicity allowing the schedule to be altered if required. In addition, the average dose intensity of cisplatin of weekly regimen was equivalent to that of three-weekly regimen. Therefore, weekly cisplatin is predicted to play an important role in the future. We thus believe that there is a need for a randomized trial comparing high-dose (100 mg/m²) three-weekly cisplatin and weekly cisplatin as a basic CRT regimen in the near future.

Funding


Conflict of interest statement

None declared.

References


