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Safety and efficacy of concurrent carboplatin plus radiotherapy for locally advanced head and neck cancer patients ineligible for treatment with cisplatin

Satoshi Hamauchi[1], Tomoya Yokota[1,*], Yusuke Onozawa[2], Hirofumi Ogawa[3], Tsuyoshi Onoe[3], Tomoyuki Kamijo[4], Yoshiyuki Iida[4], Tetsuo Nishimura[3], Tetsuro Onitsuka[4], and Hirofumi Yasui[1]

[1]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, [2]Division of Medical Oncology, Shizuoka Cancer Center, Shizuoka, [3]Division of Radiation Oncology, Shizuoka Cancer Center, Shizuoka, and [4]Division of Head and Neck Surgery, Shizuoka Cancer Center, Shizuoka, Japan

*For reprints and all correspondence: Tomoya Yokota, Division of Gastrointestinal Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo Nagaizumi Sunto-gun, Shizuoka 411-8777, Japan. E-mail: t.yokota@scchr.jp

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Abstract

Objective: Cisplatin-based chemoradiotherapy is the standard treatment for patients with locally advanced squamous cell carcinoma of the head and neck. However, patients with advanced age, renal, cardiac or neurogenic dysfunction seem ineligible for cisplatin treatment. We evaluated the safety and efficacy of concurrent carboplatin plus radiotherapy in patients ineligible for cisplatin usage.

Methods: We retrospectively analyzed the records of 25 consecutive locally advanced squamous cell carcinoma of the head and neck patients who received concurrent carboplatin plus radiotherapy at Shizuoka Cancer Center between August 2006 and March 2014. Carboplatin was administered tri-weekly or weekly.

Results: Patient characteristics were analyzed. The median age was 75 years (range, 54–82), male: female ratio, 24:1; performance status, 0–1 (23) or 2 (2); primary tumor site, oropharynx (10), hypopharynx (12), larynx (1) or oral cavity (2); Stage III (3), IVa (19) or IVb (3); induction chemotherapy, with (2) or without (23); and a median creatinine clearance of 62 ml/min (range, 37–117). The main reasons for choosing carboplatin were age (40%), renal impairment (36%) and cardiac dysfunction (20%). All patients received a planned irradiation dose of 70 Gy. Median follow-up was 30.9 months. Complete response was observed 70% patients. Median progression-free survival duration was 42.7 months. Median overall survival could not be analyzed. The 2-year progression-free and overall survival rates were 68 and 74%, respectively. The main toxicity Grade 3 or 4 was oral mucositis (56%), thrombocytopenia (34%), neutropenia (28%) and infection (24%).

Conclusions: Concurrent carboplatin plus radiotherapy is tolerated and may be an option in treating locally advanced squamous cell carcinoma of the head and neck patients ineligible for treatment with cisplatin.

Key words: head and neck neoplasms, carboplatin, chemoradiotherapy, cisplatin, carcinoma squamous cell

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Introduction

High-dose cisplatin (CDDP)-based chemoradiotherapy (CRT) has significantly improved overall survival (OS), progression-free survival (PFS) and locoregional control compared with that observed with radiotherapy (RT) alone in patients with locally advanced squamous cell carcinoma of the head and neck (LASCCHN) (1). However, high-dose CDDP administration (100 mg/m^2 on Days 1, 22 and 43) is often associated with severe nausea and vomiting, renal dysfunction and neuro- and ototoxicity. Therefore, patients who are ineligible for CDDP treatment, such as those with advanced age, renal, cardiac or neurogenic dysfunction, are often forced to use RT alone.

Carboplatin (CBDCA) is a second-generation cisplatin analog with lower gastrointestinal toxicity, nephrotoxicity and neurotoxicity compared with CDDP (2). CBDCA has been conventionally used for head and neck cancers as an alternative to CDDP, especially in patients who may have difficulty with CDDP due to its toxicity. However, the efficacy and tolerability of concurrent CBDCA plus RT is unclear for LASCCHN patients who are ineligible for CDDP treatment. In this study, we retrospectively analyzed the clinical outcomes and feasibility of concurrent CBDCA plus RT in LASCCHN patients who are ineligible for CDDP treatment.

Patients and methods

Patients

This study included patients with Stage III or IV (Union for International Cancer Control Tumor, Node, Metastasis classification, seventh Edition) head and neck squamous cell carcinoma treated with CBDCA plus RT at Shizuoka Cancer Center Hospital between August 2006 and March 2014. Patients were selected based on the following criteria:

(i) Pathologically proven squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx confirmed by computed tomography (CT) or magnetic resonance imaging (MRI)
(ii) Patients who are ineligible for CDDP treatment because of any of the following six reasons: age over 76 years, renal impairment [creatinine clearance (CCr) 40–60 ml/min], cardiac dysfunction (a history of unstable angina pectoris, myocardial infarction or chronic heart failure), neurologic impairment (peripheral neuropathy or hearing impairment), respiratory impairment (severe emphysema) or performance status (PS) of 2
(iii) No distant metastatic disease
(iv) No prior RT or surgery

The use of induction chemotherapy (ICT), not including CDDP, was acceptable for this study. Although the application of ICT was discussed by the multidisciplinary tumor board in our institution, ICT has been given to patients with a high risk of distant metastases since 2011 (3). This study was approved by the institutional review committee of the Shizuoka Cancer Center (Shizuoka, Japan) and met the standards set forth in the Declaration of Helsinki. Written informed consent was obtained from all patients in this study.

Treatment

All patients received concurrent CBDCA with conventionally fractionated RT. CBDCA was administered tri-weekly [area under the curve (AUC), 4–6 on Days 1, 22 and 43] (4) or weekly (AUC, 1.5–2 on Days 1, 8, 15, 22, 29, 36 and 43) (5,6) according to the physicians' discretion. The total dose of irradiation was 70 Gy in fractions of 2 Gy per day, 5 days per week. ICT was administered as a regimen of either CBDCA, paclitaxel (PTX) and cetuximab (Cmab) or CBDCA plus 5-fluorouracil (5FU). The CBDCA, PTX and Cmab ICT regimen consisted of CBDCA (AUC, 2; Days 1 and 8), PTX (80 mg/m^2, Days 1 and 8), and Cmab (initial dose, 400 mg/m^2; subsequent weekly doses, 250 mg/m^2; Days 1, 8 and 15). The CBDCA plus 5FU regimen consisted of CBDCA (AUC, 5; Day 1) and continuous infusion of 5FU (1000 mg/m^2, Days 1–4). ICT was repeated every 3 weeks for three cycles unless progressive disease (PD) or unacceptable toxicities were observed. Salvage surgery was performed after CRT for patients with resectable residual disease.

Evaluation

All clinical data were retrospectively obtained from medical records. Pretreatment evaluations included medical history, physical examination, laboratory tests, endoscopy, CT, MRI and [18F]-fluorodeoxyglucose positron-emission tomography/CT fusion imaging. Tumor response was assessed by CT or MRI 6–8 weeks after the completion of CRT or when clinical signs suggested PD, according to the guidelines of the Response Evaluation Criteria in Solid Tumors, version 1.1. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria, version 4.0.

Statistical analysis

PFS was calculated from the date of CRT until disease relapse, PD, death from any cause, or censored at the last follow-up visit. OS was calculated from the date of CRT until death from any cause or censored at the last follow-up visit. Survival was analyzed by the Kaplan–Meier method.

Results

Patient characteristics

Thirty patients were treated with CBDCA plus RT for LASCCHN at the Shizuoka Cancer Center between August 2006 and March 2014. Of these, five patients with paranasal sinus cancer ($n = 3$) and nasopharyngeal cancer (NPC) ($n = 2$) were excluded from this study. Our study therefore included 25 patients. Figure 1 shows a flow chart for patient selection. Baseline characteristics are shown in Table 1. The primary tumor sites were the oropharynx or hypopharynx in 88% of patients, and 88% of patients had Stage IV cancer. All patients but one received tri-weekly CBDCA plus RT and one patient did weekly CBDCA plus RT. Of two patients who received ICT, one received CBDCA and 5FU as ICT before tri-weekly CBDCA plus RT, and the other received CBDCA, PTX and Cmab before weekly CBDCA plus RT. The primary reason for choosing CBDCA plus RT is shown in Table 2. If any of the six reasons is present, we considered the patient to be ineligible for use of CDDP. The most common reason for choosing CBDCA was advanced age (median age of all patients [$n = 25$]: 75 years, median age of those who were considered to be advanced age [$n = 10$]: 78 years). The second most common reason was renal impairment [median CCr of all patients ($n = 25$): 62 ml/min, median CCr of those who were considered to have renal impairment ($n = 9$):53 ml/min], followed by cardiac dysfunction, hearing impairment, PS of 2 and severe emphysema.

Treatment compliance

All patients received irradiation with total dose of 70 Gy. The median duration of RT was 50 days (range, 46–70). Four patients had an

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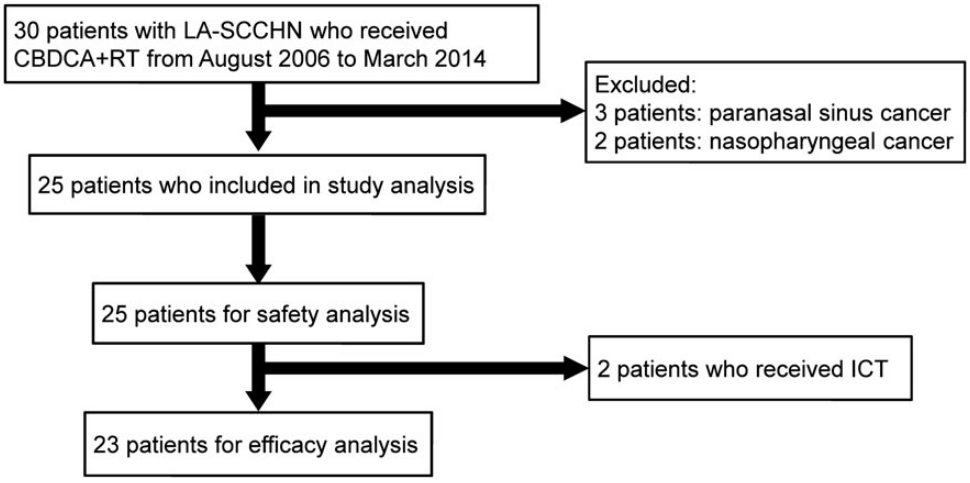

Figure 1. Patient selection criteria. A flow chart illustrating the composition of the study cohort ($n = 25$). All patients were evaluated for safety. Only patients who did not receive induction chemotherapy were evaluated for efficacy. CBDCA, carboplatin; ICT, induction chemotherapy; LA-SCCHN, locally advanced squamous cell carcinoma of the head and neck; RT, radiation therapy.

unplanned break in RT due to pneumonia ($n = 2$), sepsis ($n = 1$) or febrile neutropenia ($n = 1$). The completion rate (no dose reduction and delay) of CBDCA was 48%. Two patients (8%) delayed CBDCA due to neutropenia. Twelve patients discontinued CBDCA due to fatigue ($n = 5$), thrombocytopenia ($n = 4$) or infection ($n = 2$). Dose reductions of CBDCA starting from the second course were required for one patient (4%) due to thrombocytopenia.

Clinical response

Efficacy was evaluated in 23 patients who did not receive ICT. However, two patients died before evaluation. Complete response (CR) was observed in 70% of patients (16/23). Four patients had a partial response (PR), for a total response rate (CR plus PR) of 87% (20/23) (Table 3). Clinical response by primary tumor site was as follows: oropharynx ($n = 8$) CR:5, PR:1, PD:1, not evaluable (NE):1; hypopharynx ($n = 12$) CR:9, PR:2, NE:1; larynx ($n = 1$) CR:1; oral cavity ($n = 2$) CR:2. Two patients underwent salvage surgery for residual neck disease at 15 weeks and 27 weeks after completion of RT, respectively. Though one patient developed post-operative bleeding from a neck lesion, bleeding was stopped by applying direct pressure and the patient was discharged on the third day post-operation.

Among 16 complete responders, one patient relapsed in the pituitary gland at 18 months after the completion of RT. Of the four partial responders, two patients had persistent neck disease and primary lesions. Of these, one patient received chemotherapy (5FU plus CDDP) and the other was treated with best supportive care. The remaining two patients with persistent neck disease without primary lesions underwent salvage neck dissection. Only one patient was evaluated with PD in the neck disease at 6 weeks after RT completion. The patient did not receive subsequent treatment due to poor PS and died 10 weeks after the diagnosis of PD.

Survival

The median follow-up period was 30.9 months (range, 14.3–65.8). Median PFS was 42.7 months (Fig. 2). Median OS has not yet been reached (Fig. 3). The PFS and OS rates at 2 years were 68 and 74%, respectively. Up to January 2015, the causes of death in nine patients were disease progression ($n = 4$), asphyxiation ($n = 3$) or pneumonia ($n = 2$).

Toxicity

The worst toxicities observed during CRT are listed in Table 4. Grade 3 or 4 hematological toxicities were neutropenia (28%), anemia (36%) and thrombocytopenia (34%). The non-hematological toxicities Grade 3 was noted for oral mucositis (56%) and infection (24%). Other Grade 3 non-hematological toxicities included anorexia ($n = 1$, 4%), dermatitis radiation ($n = 1$, 4%) dysphagia ($n = 1$, 4%), and an increase in alanine aminotransferase ($n = 1$, 4%). No non-hematological toxicities Grade 4 were observed. Two patients (8%) died within 30 days after completing RT or CBDCA administration. Of these, one patient died of acute bacterial pneumonia, which occurred 2 days after RT completion. The other patient died of bleeding from a primary lesion, which occurred 5 days after RT completion.

Discussion

Since there is no standard therapy for LASCCHN patients who are ineligible for high-dose CDDP treatment, RT alone is often chosen for in clinical practice. However, the outcome of RT monotherapy for LASCCHN remained unfavorable (CR rate, 22–29%; 3-year survival, 7–45%) (1,7–10). Several studies have reported on the use of weekly low-dose CDDP plus RT for LASCCHN (11–13). Although there are no head-to-head randomized studies directly compared tri-weekly CDDP plus RT with weekly CDDP plus RT for LASCCHN, weekly CDDP plus RT seems to have less renal toxicity (Grade 3 or 4 in 0%) (11,13) and neurotoxicity (Grade 3 or 4 in 0–3%) (11,13) than tri-weekly CDDP plus RT (Grade 3 or 4 renal toxicity in 2–9%, Grade 3 or 4 neurotoxicity in 7%) (1,14,15). However, it is unclear whether weekly CDDP plus RT for our study population is safe or not. Indeed the inclusion criteria of these studies were median age of 44–59, PS of 0–1/Karnofsky performance status (KPS) of 70–100, normal organ function and no history of neuropathy. Therefore, RT plus non-CDDP chemotherapy may be appropriate to achieve better survival and safety in these patients. However, there are no prospective studies for LASCCHN patients who are ineligible for treatment with CDDP.

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Table 1. Patient characteristics ($n = 25$)

	Number of patients
Gender A	
Male	24
Female	1
Median age, years (range)	75 (54–82)
PS (ECOG)	
0,1	23
2	2
Primary site	
Oropharynx	10
Hypopharynx	12
Larynx	1
Oral cavity	2
T stage	
T1	2
T2	7
T3	4
T4a	10
T4b	2
N stage	
N0	4
N1	1
N2a	1
N2b	14
N2c	4
N3	1
Disease stage	
III	3
IVa	19
IVb	3
Resectability[a]	
Resectable	18
Unresectable	7
Induction chemotherapy	
Yes	2
No	23
CBDCA administration	
Tri-weekly	24
Weekly	1
Histologic type	
Well-differentiated SCC	3
Moderately differentiated SCC	9
Poorly differentiated SCC	3
Unknown	10
Smoking history	
≥10 pack-years	23
<10 pack-years	2
Creatinine clearance[b] (ml/min) [median (range)]	62 (37–117)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; SCC, squamous cell carcinoma; CBDCA, carboplatin.

[a]The multidisciplinary tumor board decided upon tumor resectability.

[b]Creatinine clearance was calculated according to Cockcroft–Gault equation.

Table 2. Primary reason for choosing carboplatin plus radiation therapy ($n = 25$)

	Number of patients[a] (%)
Age over 76 years old	10 (40)
Renal impairment	9 (36)
Cardiac depression	5 (20)
Hearing impairment	2 (8)
PS of 2	2 (8)
Severe emphysema	1 (4)

[a]Partially duplicated data.

Table 3. Clinical response to chemoradiotherapy ($n = 23$)

Complete response, *n* (%)	16 (70)
Partial response, *n*	4
Stable disease, *n*	0
Progressive disease, *n*	1
Overall response, *n* (%)	20 (87)
Not assessable, *n*	2

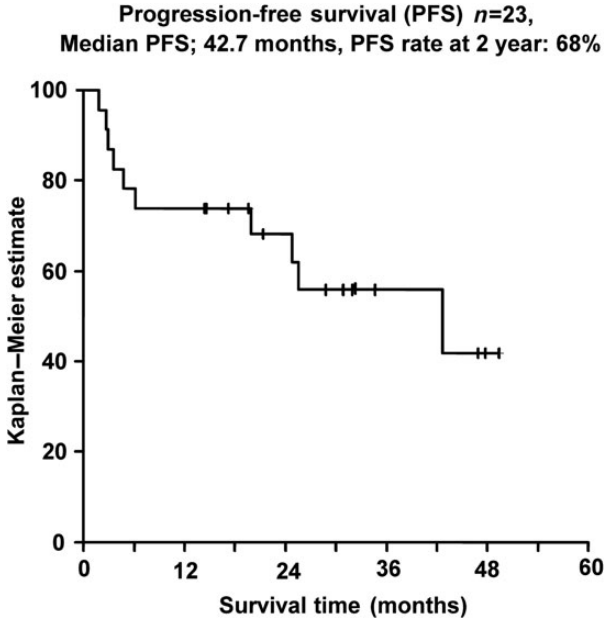

Figure 2. Kaplan–Meier plot showing progression-free survival ($n = 23$). MST, median survival time.

In addition to CDDP, Cmab, a monoclonal antibody targeting the epidermal growth factor receptor, is an anti-tumor drug used in combination with RT in patients with LASCCHN. A study by Bonner et al. (10) demonstrated that Cmab plus RT significantly improved OS, PFS and locoregional control compared with RT alone. However, Cmab plus RT does not seem to be the standard therapy for LASCCHN, as Cmab plus RT has never been prospectively compared with tri-weekly CDDP plus RT in a randomized Phase III study. Furthermore, no prospective trials of Cmab plus RT have been conducted in patients who are ineligible for CDDP treatment. The study by Bonner et al. included patients with normal organ function, high KPS and younger age. As for adverse events, Cmab plus RT led to a greater number of Grade 3 or 4 skin reactions than those receiving RT alone (35.1 versus 21.2%, $P < 0.05$), although there were few cases with nausea, vomiting, renal dysfunction and neuro- and ototoxicity (16). Other studies have also observed Grade 3 or 4 radiation dermatitis in over 30% of patients treated with Cmab plus RT (17,18). Severe skin toxicity could reduce the patient's quality of life and may sometimes lead to treatment discontinuation and dose reduction. Taken together, the

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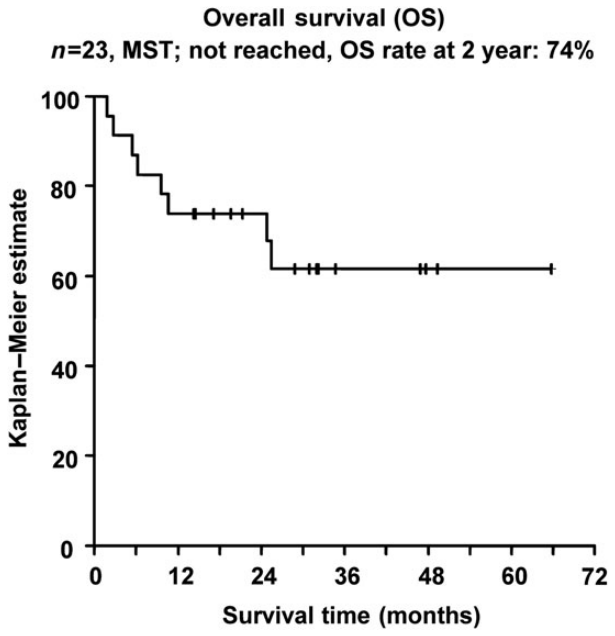

Figure 3. Kaplan–Meier plot showing overall survival ($n = 23$).

Table 4. Summary of toxicity during chemoradiotherapy ($n = 25$)

	All Grades		Grade 3		Grade 4	
	n	(%)	*N*	(%)	*n*	(%)
Hematologic toxicity						
Neutrophil count decreased	22	88	5	20	2	8
Anemia	25	100	9	36	0	0
Platelet count decreased	22	88	4	16	4	16
Non-hematologic toxicity						
Mucositis oral	25	100	14	56	0	0
Anorexia	18	72	1	4	0	0
Nausea	6	24	0	0	–	–
Vomiting	3	12	0	0	0	0
Fatigue	20	80	0	0	–	–
Radiation dermatitis	25	100	0	0	0	0
Dry mouth	25	100	0	0	0	0
Dysgeusia	17	68	–	–	–	–
Dysphagia	15	60	1	4	0	0
Hearing impaired	1	4	0	0	0	0
Peripheral sensory neuropathy	0	0	0	0	0	0
Trismus	1	4	0	0	–	–
Infection	6	24	6	24	0	0
AST increase	14	56	0	0	0	0
ALT increase	13	52	1	4	0	0
Creatinine increase	11	44	0	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

currently available data do not support the use of Cmab plus RT as an alternative to RT alone in patients who cannot tolerate CDDP.

In a prospective randomized study in patients with locally advanced NPC, concurrent CBDCA (100 mg/m^2 on Days 1, 8, 15, 22, 29 and 36) plus RT demonstrated comparable efficacy and better tolerability when compared with concurrent CDDP (100 mg/m^2 on Days 1, 22 and 43) plus RT (5). There was no significant difference in the 3-year disease-free survival (61 vs 63% for the CBDCA and CDDP regimens, respectively) or 3-year OS (79 vs 78%, respectively). For non-nasopharyngeal LASCCHN, a randomized three-arm Phase III study was conducted to compare the 3-year survival rate with RT alone (total dose, 70 Gy), concurrent CDDP (100 mg/m^2 on Days 2, 22 and 42) plus RT, and concomitant CBDCA (AUC, 7 on Days 2, 22 and 42) plus RT (4). This study showed that platinum-based CRT significantly prolonged 3-year survival compared with RT alone (42, 52 and 17.5% for CBDCA, CDDP and RT alone, respectively).

There is no specific consensus of ineligibility for the use of (high-dose) CDDP. Therefore, we determined the ineligible criteria in our study based on the toxicity of CDDP and on the inclusion or exclusion criteria of clinical trial using CDDP for head and neck cancer. As a result, we listed six factors in the Patients and Methods section. CBDCA has less renal-, gastrointestinal- neurotoxicity, and no requirement for large hydration, compared with CDDP. Therefore, we would think CBDCA is safer than CDDP for those who meet our criteria. In our study, although all patients were considered to be ineligible for CDDP treatment, mainly due to advanced age or renal impairment, they were able to receive a total dose of 70 Gy of irradiation. Furthermore, 70% of these patients were able to achieve CR, despite the high proportion of Stage IV (88%) and unresectable cases (30%). These results suggest that CBDCA plus RT achieved excellent treatment outcomes compared with RT monotherapy. In terms of safety, there was no Grade 3 or 4 neurotoxicity, nephrotoxicity, nausea or vomiting. The frequency of skin toxicity (4% of Grade 3 radiation dermatitis) was lower than that with Cmab plus RT in a study by Bonner et al.

However, discontinuation or dose reduction of CBDCA was necessary due to myelotoxicity in our patients. Four patients developed infection, including two (12%) with pneumonia, one (6%) with a catheter-related bloodstream infection and one (6%) with febrile neutropenia. All of these patients received a CBDCA dose of AUC = 5. Except in the patient with a catheter-related bloodstream infection, the cases were associated with neutropenia at the onset of infection. Jodrell et al. (19) showed a significant relationship between administered AUC dose of CBDCA and the likelihood of thrombocytopenia and leukopenia. Therefore, care should be taken to prevent myelotoxicity caused by high doses of CBDCA that results in infection. Low-dose weekly CBDCA plus RT may reduce the risk of myelotoxicity.

There are no clinical studies comparing tri-weekly CBDCA plus RT with weekly CBDCA plus RT. In the aforementioned prospective study for locally advanced NPC, weekly CBDCA plus RT was equally effective as tri-weekly CDDP plus RT and caused Grade 3 or 4 leukopenia in 10% and Grade 3 or 4 thrombocytopenia in 8% of patients (5). Tri-weekly CBDCA plus RT caused Grade 3 or 4 leukopenia in 18% and Grade 3 or 4 thrombocytopenia in 27% of patients (4). These results suggest that weekly CBDCA plus RT may lead to milder myelotoxicity compared with tri-weekly CBDCA plus RT and may be an alternative treatment to tri-weekly CBDCA plus RT for LASCCHN. In our study, most patients (96%) have received tri-weekly CBDCA plus RT since 2006 by referencing the prospective trial on tri-weekly CBDCA plus RT for head and neck cancer. However, tri-weekly CBDCA caused severe myelotoxicity (Grade 3 or 4 leukopenia in 28% and Grade 3 or 4 thrombocytopenia in 32% of patients), which subsequently leads to infection. Therefore, the use of weekly CBDCA plus RT is increasing recently in our hospital due to its mild bone marrow toxicity. However, the patients recently treated with weekly CBDCA plus RT were excluded from our study because of the shortness of follow-up time.

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In conclusion, CBDCA plus RT is feasible and may be an option for treatment of LASCCHN patients who are ineligible for CDDP treatment. Although this study has limitations, such as a small number of patients, use of retrospective data and performance at a single center, this is the first report to evaluate the efficacy and feasibility of CBDCA plus RT in patients with LASCCHN who are ineligible for CDDP treatment. Therefore, our observations should be confirmed with a prospective investigation.

Conflict of interest statement

Tomoya Yokota serves in an advisory role at AstraZeneca, Merck Serono and Bristol-Myers Squibb, and has received lecture fees from Merck Serono and Bristol-Myers Squibb.

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