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ORIGINAL RESEARCH

Retrospective analysis of chronomodulated chemotherapy versus conventional chemotherapy with paclitaxel, carboplatin, and 5-fluorouracil in patients with recurrent and/or metastatic head and neck squamous cell carcinoma

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Background: Chronomodulated chemotherapy has emerged as a new therapy as a result of recent studies focusing on the biological clock. It has been demonstrated that combination chronomodulated chemotherapy of platinum-based drugs and 5-fluorouracil (5-Fu) can significantly improve efficacy and reduce the incidence of adverse events in patients with metastatic colorectal cancer, as compared with conventional chemotherapy. However, the results may be different in different tumors. Recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) is very difficult to treat, with an extremely unfavorable prognosis. So far, no report is available on chronomodulated chemotherapy for HNSCC.

Methods: Retrospective analyses were made on 49 patients with local recurrent and/or metastatic HNSCC who underwent palliative treatments with paclitaxel, carboplatin, and 5-Fu. The patients were divided into a chronomodulated chemotherapy group (28 patients) and a conventional chemotherapy group (21 patients) according to their administration times. The two groups were compared for tumor objective response rate, overall survival (OS), progression-free survival (PFS), and the incidence of adverse events.

Results: The tumor objective response rate and patients' OS were significantly higher and longer in the chronomodulated chemotherapy group than in the conventional chemotherapy group (71.43% versus 42.86%, respectively, $P<0.05$; and median OS 15.3 months versus 10.6 months, respectively, $P<0.05$). However, PFS was similar statistically (median PFS 11.6 months versus 7.2 months, $P>0.05$). The global incidence of adverse events in the chronomodulated chemotherapy group was significantly lower than that in the conventional chemotherapy group (46.43% versus 76.19%, $P<0.05$), with significantly lower incidence of grade 3–4 adverse events (7.14% versus 33.33%, $P<0.05$).

Conclusion: Chronomodulated chemotherapy with paclitaxel, carboplatin, and 5-Fu may be a new and effective therapy for patients with recurrent and/or metastatic HNSCC as compared with conventional chemotherapy.

Keywords: chronotherapy, chronomodulated chemotherapy, head and neck cancer, palliative chemotherapy, paclitaxel, 5-fluorouracil, carboplatin

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Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for about 3% of systemic malignancies.[1] For early stage HNSCC patients, either surgery or radiotherapy alone is effective enough to attain 5-year survival in 60%–90% of patients.[2] However, for

advanced HNSCC, comprehensive therapies including chemotherapy, surgery, radiotherapy, and their combinations are needed. Even after the combined therapies, the 3-year and 5-year survival rates have been found to be between 30%–50% and 10%–30%, respectively.[2–4] Moreover, studies also found that local recurrence and distant metastasis rates in these patients were between 50%–60% and 20%–30%, respectively.[2,4] It has been shown that patients with recurrent and metastatic HNSCC are very difficult to treat and have very unfavorable prognoses.[5] Although a few patients with locoregional recurrent HNSCC may respond well to surgery or reirradiation, the majority of patients can be only treated palliatively due to a number of technical and personal factors, such as technical unresectability, low surgical curability, incompatibility with reirradiation, patient's confidence loss for further treatment, organ preservation, and expense concerns.[3] Chemotherapy is currently the most commonly used palliative treatment and has been demonstrated to be able to improve the patients' quality of life and prolong their survival to a certain extent.[3,6] Previous studies have shown that palliative treatments using platinum-based drugs in combination with 5-fluorouracil (5-Fu) can significantly improve the survival of patients with recurrent and metastatic HNSCC, with the median overall survival (OS) and tumor objective response rate (ORR) being only 6–8 months and 32%, respectively.[7,8] Combination therapies of taxanes, platinum-based drugs, and 5-Fu have been confirmed to be more effective to treat HNSCC than other chemotherapies and have been recognized as first-line chemotherapy.[9–12] However, after palliative treatment, the median OS and tumor ORR were only 9–11 months, and 44%, respectively, for patients with recurrent and metastatic HNSCC.[4,13] Therefore, it is of great significance to explore new and effective therapies for patients with recurrent and metastatic HNSCC in order to improve their survival time and quality of life.

Previous studies have shown that in both normal and tumor cells there is a clear 24-hour circadian rhythm for cell growth and proliferation, DNA synthesis, and activities of drug catabolic enzymes in humans. However, there are differences in the circadian rhythms of cell proliferation and DNA synthesis between tumor cells and normal marrow or gastrointestinal epithelial cells. The efficacy and the incidence of adverse events have been found to differ significantly among over 30 anticancer drugs analyzed due to their different administration times.[14–17] The difference in the efficacy and incidence of adverse events for the same dose of the drugs could be as large as twofold when given at different times during the day or at night.[15] Chronomodulated chemotherapy has been proposed as a way to provide timely optimized medication to achieve maximum efficacy with minimum adverse effect to improve a patient's survival time and quality of life, and it is based on the differences in circadian rhythms of cell growth, DNA synthesis, etc between the normal and tumor cells.[14,17]

Earlier studies have shown that taxanes (such as paclitaxel and docetaxel), platinum-based drugs (such as cisplatin, carboplatin, and oxaliplatin), and antimetabolic drugs (such as 5-Fu) are suitable for chronotherapy.[14,18–23] Platinum drugs given in the afternoon and 5-Fu continuously infused at night were reported to significantly reduce adverse events as compared with conventional chemotherapy for patients with metastatic colorectal cancer and non-small cell lung cancer, and also to improve survival times for patients with metastatic colorectal cancer.[21–23] Studies also found that taxanes given in the middle of resting phase could significantly improve drug tolerability and antitumor efficacy in mice transplanted with pancreatic and mammary tumors.[18,19] However, it has been noted that the changes in the circadian rhythms for growth and proliferation in different types of tumors are often different.[24] Therefore, administration of drugs at different times for different cancers may not produce the same results. Furthermore, so far, there are only a handful of reports on chronomodulated chemotherapy for a limited number of cancers. No report on chronomodulated chemotherapy is available for HNSCC, but chronotherapy provides a new direction for the treatment of recurrent and metastatic HNSCC.

In this study we retrospectively analyzed the data from patients with recurrent and/or metastatic HNSCC who underwent chronomodulated chemotherapy and conventional chemotherapy between January 2005 and December 2008. These patients were treated with three drugs: paclitaxel, carboplatin, and 5-Fu. The analysis evaluated the efficacy and adverse events in the two therapies in order to provide a more effective palliative therapy option for patients with recurrent and metastatic HNSCC.

Materials and methods

Patients

In this single-institutional study, medical records for all HNSCC patients admitted to the Department of Oral and Maxillofacial Surgery, the First Affiliated Hospital of Chongqing Medical University between January 2005 and December 2008 were retrieved and reviewed. Patients who fulfilled the following criteria were included in the study: 1) pathologically confirmed diagnosis of local recurrent and/or metastatic HNSCC; 2) had received only two or more

than two courses of palliative combination chemotherapy with paclitaxel, carboplatin, and 5-Fu.

Data collection and efficacy variables

All patients' medical data and follow-up records were obtained from the inpatient electronic medical records system at the hospital. The data included general patient information (such as age, sex), site and stage of the tumor, history of previous treatment, tumor responses, adverse events, OS and progression-free survival (PFS), etc. Measurable lesions were detected by computed tomography (CT) or magnetic resonance imaging (MRI). Tumor responses achieved were calculated according to World Health Organization (WHO) criteria for complete response, partial response, stable disease, and progressive disease. Complete response + partial response was used to calculate ORR.[25] The initial assessments were made two courses after chemotherapy, followed by assessments once per course. CT or MRI review was conducted 1–2 months after each treatment. For patients suspected to have disease progression, CT or MRI review was conducted ahead of the regular schedule. Chemotherapy-related adverse events were classified according to WHO toxicity grading criteria for anticancer drugs.[26] Follow-up visits were made once every 1–3 months in the first year, once every 2–4 months in the second year, and once every 4–6 months in the third year of the treatments.

Chemotherapeutic regimen

Patients were divided into two groups according to their chemotherapeutic schedules, namely, chronomodulated chemotherapy group and conventional chemotherapy group. In the former group, patients were given continuous intravenous infusion of paclitaxel (150 mg/m^2) on the first day from 3–5 am, carboplatin (350 mg/m^2) on the first day from 4–8 pm, and 5-Fu (800 mg/m^2) from the first day to the fifth day from 10 pm to 7 am. In the latter group, these drugs were given at the same doses as in the chronomodulated chemotherapy group, but within normal working hours, started between 9–11 am and completed before 5.30 pm.

Before paclitaxel infusion, dexamethasone, diphenhydramine, and cimetidine were given as usual as the pretreatment to prevent paclitaxel-related allergic reactions. The above courses were repeated every 3–4 weeks up to six times, unless they were refused by the patient, or stopped due to the occurrence of intolerable adverse events or disease progression during the therapeutic periods.

This study was approved by the Biomedicine Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. The chemotherapeutic schedule was selected by each patient, and a written informed consent was obtained from each patient prior to treatment.

Statistical analysis

Data were processed and statistically analyzed using SPSS statistical software version 13 (IBM Corporation, Armonk, NY, USA). OS was calculated from the date to receive the first course of chemotherapy until death. PFS was computed as the time from receiving the first course of chemotherapy to disease progression or death, whichever occurred first. The Kaplan–Meier method was used for survival analysis. The differences between the groups were determined using the log-rank test. Comparison between rates was carried out using the chi-square test or Fisher's exact test, means were compared using the *t*-test, and differences were considered statistically significant at $P<0.05$.

Results

Patient baseline characteristics

In total, 49 HNSCC patients fulfilling the selection criteria were identified. The patients consisted of 36 males and 13 females, aged between 40–78 years with median and mean ages of 56 years and 57.1 years, respectively. The primary tumor sites included tongue (eleven patients), cheek (six patients), gum (six patients), mouth floor (nine patients), palate (two patients), and oropharynx (15 patients). 28 patients were given chronomodulated chemotherapy and 21 patients received conventional chemotherapy. There was no statistically significant difference between the two groups in age, sex, site of primary tumor, tumor location, history of previous therapy, and stage of the previous disease (Table 1). Patients were followed up for 5–36 months, with a median of 15 months and an average of 17.3 months.

Treatment

For the chronomodulated chemotherapy group, the patients completed 3–6 courses of the treatment, with a median of 5 courses and an average of 5.1 courses. For the conventional chemotherapy group, the patients completed 2–6 courses, with a median of 5 courses, and an average of 4.8 courses. The numbers of treatment courses were statistically similar between the two groups (t=0.884, P=0.381).

Tumor response

The tumor ORR was 71.43% and 42.86% in the chronomodulated chemotherapy group and the conventional chemotherapy group, respectively. The rate in the former group

Table 1 Characteristics of the patients and tumors included in the study

Variables	Chronomodulated chemotherapy group (n=28)	Conventional chemotherapy group (n=21)	*P*-value*
Age (years)			0.877
Median	56	54	
Range	41–78	40–75	
Sex (n [%])			0.709
Male	20 (71)	16 (76)	
Female	8 (29)	5 (24)	
Site of primary tumor (n [%])			0.877
Tongue	6 (21)	5 (24)	
Cheek	4 (14)	2 (10)	
Gums	2 (7)	4 (19)	
Mouth floor	6 (21)	3 (14)	
Palate	1 (4)	1 (5)	
Oropharynx	9 (32)	6 (29)	
Tumor location (n [%])			0.910
Local recurrence	8 (29)	5 (24)	
Local recurrence and cervical lymph metastasis	7 (25)	5 (24)	
Local recurrence and distant metastasis	5 (18)	4 (19)	
Local recurrence, cervical lymph metastasis, and distant metastasis	3 (11)	1 (5)	
Cervical lymph metastasis and/or distant metastasis	5 (18)	6 (29)	
Previous therapy (n [%])			0.926
Surgery or chemoradiotherapy	5 (18)	3 (14)	
Induction chemotherapy + radiotherapy	1 (4)	1 (5)	
Surgery + chemoradiotherapy	15 (54)	10 (48)	
Induction chemotherapy + surgery + chemoradiotherapy	7 (25)	7 (33)	
Stage of previous disease (n [%])			0.720
III	8 (29)	7 (33)	
IV	20 (71)	14 (67)	

Note: *Represents *P*-values were calculated from chi-square test, Fisher's exact test, or *t*-test.

was significantly higher than in the latter group (χ^2=4.055, *P*=0.044) (Table 2).

Overall survival and progression-free survival

The median OS was 15.3 months (95% confidence interval [CI] 11.0–19.6 months) in the chronomodulated chemotherapy group and 10.6 months (95% CI 5.5–15.7 months) in the conventional chemotherapy group. The former was significantly longer than the latter (log-rank χ^2=4.044, *P*=0.044) (Figure 1). The median PFS was 11.6 months (95% CI 8.1–15.1 months) and 7.2 months (95% CI 3.2–11.2 months) in the two groups, respectively, not significantly different from each other (log-rank χ^2=3.310, *P*=0.069) (Figure 2).

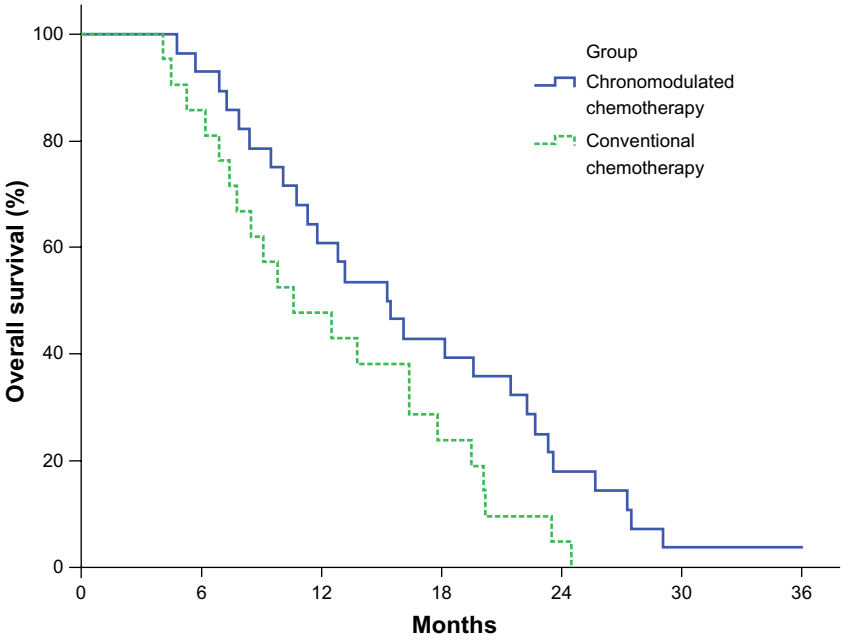
Table 2 Tumor response among 49 patients

Groups	Number of patients	Tumor response				ORR
		CR	PR	SD	PD	CR + PR (%)
Chronomodulated chemotherapy	28	4	16	6	2	71.43
Conventional chemotherapy	21	1	8	8	4	42.86
Total	49	5	24	14	6	59.18

Notes: *P*-values were calculated from chi-square test. The difference of ORR in chronomodulated chemotherapy was significantly higher than in the conventional chemotherapy group (*P*=0.044).
Abbreviations: CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Adverse events

Adverse events in the patients are shown in Table 3. No allergy was observed. The adverse event incidence rates in hematologic toxicity were significantly lower (χ^2=5.743, *P*=0.017) in the chronomodulated chemotherapy group (32.14% [9/28]) than that in the conventional chemotherapy group (66.67% [14/21]). Adverse events mainly included anemia, leukopenia, neutropenia, and thrombocytopenia. The adverse event incidence rates in nonhematologic toxicity were also statistically significantly different (χ^2=5.444, *P*=0.020) in the two groups (42.86% [12/28] versus 76.19% [16/21], respectively). The adverse events were mainly stomatitis,



Number at risk							
Chronomodulated chemotherapy	28	26	17	12	5	1	1
Conventional chemotherapy	21	18	10	5	1	0	0

Figure 1 The Kaplan–Meier survival analysis for overall survival.
Notes: The median overall survival for chronomodulated chemotherapy and conventional chemotherapy groups was 15.3 months and 10.6 months, respectively, with 95% confidence intervals ranging from 11.0–19.6 and 5.5–15.7 months in the former and latter groups, respectively. *P*-value from the log-rank test for chronomodulated chemotherapy versus conventional chemotherapy is *P*=0.044.

nausea, vomiting, alopecia, and peripheral neurotoxicity. Overall, the adverse event incidence rates were 46.43% (13/28) and 76.19% (16/21) in the two groups, with the rate in the chronomodulated chemotherapy group significantly lower than that in the conventional chemotherapy group (χ^2=4.400, *P*=0.036). Grade 3–4 adverse event incidence rates were 7.14% (2/28) and 33.33% (7/21) in the two groups, respectively. The former was significantly lower than the latter (χ^2=3.882, *P*=0.049). All the patients with grade 1–2 adverse events were fully recovered after symptomatic treatments. A few patients with grade 3–4 adverse events had their chemotherapy postponed for their treatments.

Discussion

Lévi et al reported that in comparison with conventional chemotherapy, chronomodulated chemotherapy for patients with metastatic colorectal cancer, using continuous infusion of oxaliplatin in the afternoon and 5-Fu at night, significantly increased tumor ORR (53% versus 32%, respectively, $P<0.05$) and survival times (median OS was 19 months and 14.9 months, respectively, $P<0.05$), with significant reduction in adverse events.[21] Continuous infusion of carboplatin in the afternoon and 5-Fu at night has been demonstrated to significantly reduce the incidence of adverse events and improve the life quality of surviving patients with advanced non-small cell lung cancer when the two therapies were compared.[22,23] In animal models, Tampellini et al and Granda et al have proved that taxanes given in the middle of resting phase significantly improve the efficacy and reduce the adverse events for pancreatic and breast cancers.[18,19] Although only a few reports are available on chronomodulated chemotherapy so far, it is clear that the therapy shows promise in improving the treatment efficacy and reducing adverse events and should be considered as one of the new options for HNSCC treatment.

In this study, we retrospectively compared the efficacy and adverse events in patients with recurrent and/or metastatic HNSCC treated with the three-drug combination palliative chronomodulated chemotherapy and the conventional chemotherapy. The results showed that chronomodulated chemotherapy treatment was significantly more effective in improving tumor ORR than the conventional chemotherapy (71.43% versus 42.86%, $P<0.05$). In the former group, the patients' OS was also significantly longer than that in the

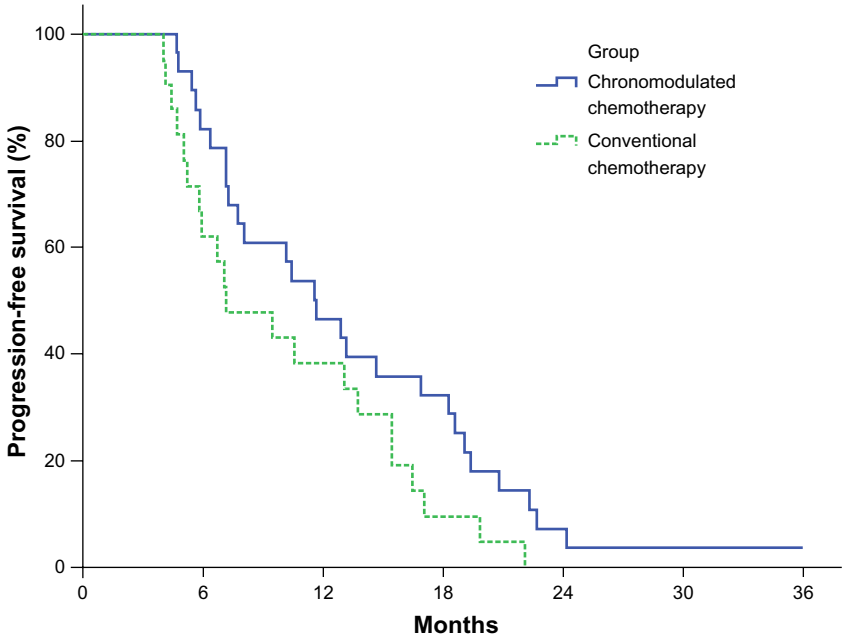


Figure 2 The Kaplan–Meier survival analysis for progression-free survival.
Notes: The median progression-free survival for the chronomodulated chemotherapy and conventional chemotherapy groups was 11.6 months and 7.2 months, respectively, with 95% confidence intervals ranging from 8.1–15.1 and 3.2–11.2 months, in the former and latter groups, respectively. *P*-value from the log-rank test for chronomodulated chemotherapy versus conventional chemotherapy is *P*=0.069.

Table 3 Adverse events following the chemotherapies

Adverse events	Chronomodulated chemotherapy (n=28)		Conventional chemotherapy (n=21)		*P***	*P****
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4		
Hematologic toxicity						
Anemia	10.71% (3/28)	0%	33.33% (7/21)	0%	0.113	–
Leukopenia	28.57% (8/28)	3.57% (1/28)	33.33% (7/21)	28.57% (6/21)	0.038	0.039
Neutropenia	21.43% (6/28)	3.57% (1/28)	42.86% (9/21)	14.29% (3/21)	0.022	0.407
Thrombocytopenia	25% (7/28)	0%	38.10% (8/21)	9.52% (2/21)	0.100	0.179
All events in hematologic toxicity*	32.14% (9/28)		66.67% (14/21)		0.017	
Nonhematologic toxicity						
Liver function abnormality	10.71% (3/28)	0%	23.81% (5/21)	0%	0.403	–
Stomatitis	17.86% (5/28)	0%	14.29% (3/21)	23.81% (5/21)	0.112	0.025
Nausea and vomiting	42.86% (12/28)	0%	47.62% (10/21)	28.57% (6/21)	0.020	0.010
Diarrhea	0%	0%	0%	0%	–	–
Gastrointestinal bleeding	0%	0%	0%	0%	–	–
Nephropathy	7.14% (2/28)	0%	19.05% (4/21)	0%	0.414	–
Fever	7.14% (2/28)	0%	23.81% (5/21)	0%	0.216	–
Allergy	0%	0%	0%	0%	–	–
Skin toxicity	0%	0%	0%	0%	–	–
Alopecia	3.57% (1/28)	3.57% (1/28)	28.57% (6/21)	9.52% (2/21)	0.021	0.796
Peripheral neurotoxicity	21.43% (6/28)	0%	42.86% (9/21)	0%	0.107	–
All events in nonhematologic toxicity*	42.86% (12/28)		76.19% (16/21)		0.020	
Total grade 3–4 events (%)*	7.14% (2/28)		33.33% (7/21)		0.049	
Total events (%)*	46.43% (13/28)		76.19% (16/21)		0.036	

Notes: *Represents patients who were counted for multiple events; **represents *P*-values which were from chi-square test for the differences in grade 1–4 events between the therapy groups; ***represents *P*-values which were from chi-square test or Fisher's exact test for the differences in grade 3–4 events between the therapy groups.

latter group (median overall survival 15.3 months versus 10.6 months, $P<0.05$), but PFS in the two groups did not significantly differ ($P>0.05$).

We found that in the conventional chemotherapy group, the incidence rates of all adverse events and grade 3–4 adverse events were 76.19% (16/21) and 33.33% (7/21), respectively. While in the chronomodulated chemotherapy group, these figures were significantly lower (46.43% [13/28] and 7.14% [2/28], respectively). Further analysis on hematologic toxicity indicated that fewer patients in the chronomodulated chemotherapy group had leukopenia and neutropenia than in the conventional chemotherapy group (32.14% versus 61.91%, respectively, [$P<0.05$] for leukopenia and 25% versus 57.14%, respectively, [$P<0.05$] for neutropenia). Furthermore, grade 3–4 leukopenia was also significantly lower in the former than in the latter (3.57% versus 28.57%, $P<0.05$). However, no significant difference between the two groups was found in the incidence of thrombocytopenia. For nonhematologic toxicity, significantly fewer patients in the chronomodulated chemotherapy group had nausea and vomiting and alopecia than in the conventional chemotherapy group (42.86% versus 76.19%, respectively, [$P<0.05$] for nausea and vomiting and 7.14% versus 38.10%, respectively, [$P<0.05$] for alopecia). Meanwhile, none of the patients in the former group had grade 3–4 nausea and vomiting (0% versus 28.57%, $P<0.05$). Although the overall incidence of stomatitis between the two groups was similar, none of the former group had grade 3–4 stomatitis (0% versus 23.81%, $P<0.05$). Therefore, patients were more tolerant to chronomodulated chemotherapy than to conventional chemotherapy, suggesting that chronomodulated chemotherapy could improve patient quality of life.

Chronomodulated chemotherapy and conventional chemotherapy are carried out in the same chemotherapeutic regimen except for drug administration schedules. On the other hand, during night chemotherapy, the patients' rest should be disturbed as little as possible.

Conclusion

We have demonstrated that in comparison with conventional chemotherapy, chronomodulated chemotherapy with paclitaxel, carboplatin, and 5-Fu significantly improved the tumor ORR, increased OS, and reduced the incidence of adverse events for patients with recurrent and/or metastatic HNSCC. The results from this study provide evidence supporting the use of palliative chronomodulated chemotherapy for patients with recurrent and/or metastatic HNSCC. However, this work was based on a relatively small number of patients (49 patients). Further prospective study with a large sample size is needed to draw a more solid conclusion.

Disclosure

The authors report no conflicts of interest in this work.

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