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ORIGINAL ARTICLE

Effectiveness of pharmacokinetic modulating chemotherapy combined with cisplatin as induction chemotherapy in resectable locally advanced head and neck cancer: phase II study

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Abstract
Purpose To test the efficacy and safety of pharmacokinetic modulating chemotherapy combined with cisplatin (PMC-cisplatin) as induction chemotherapy (ICT) before definitive treatment in patients with respectable locally advanced head and neck squamous cell carcinoma (HNSCC).
Patients and methods Patients with stage III–IV resectable locally advanced HNSCC were enrolled. All eligible patients received PMC-cisplatin regimen as ICT containing intravenous leucovorin 250 mg/m^2 and 5-FU 600 mg/m^2 on day 1, oral tegafur–uracil (UFUR®) 250 mg/m^2/day on days 1–5, repeated every week for six courses. Cisplatin 100 mg/m^2 was given during the first and fourth courses of PMC. For ICT responders, concurrent chemoradiotherapy (CRT) with cisplatin/tegafur–uracil/70 Gy radiotherapy was performed. Salvage surgery plus postoperative CRT was given to ICT non-responders.
Results The overall response rate of PMC-cisplatin as ICT was 76%, including a complete remission rate of 23%. The overall organ preservation rate of the multimodality treatment was 75%, with 97% in ICT responders. At a median follow-up of 25 months, 47% of the patients were still alive and disease-free. The superiority of disease-free survival was demonstrated in ICT responders. The 3-year overall survival rate was 67%. The toxicity of treatment was acceptable.
Conclusions Application of PMC-cisplatin as the induction chemotherapy before definitive treatment provides a promising result in treatment response and survival of advanced HNSCC. This regimen is effective and safe, and further studies considering the combination of PMC with other chemotherapeutics such as taxanes to improve the clinical outcome of advanced HNSCC is warranted.

Keywords Head and neck cancer · Induction chemotherapy · Organ preservation · Pharmacokinetic modulating chemotherapy

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Introduction

Carcinomas of the head and neck, including cancers originating from the oral cavity, oropharynx, hypopharynx and larynx, represent the sixth most common type of cancer in the world [1], and rank the fourth in male cancer-related deaths in Taiwan [2] due to the habitual consumption of betel nuts [3]. More than 90% of head and neck cancers are squamous cell carcinoma (HNSCC), and 60% of patients are present with advanced disease (stages III and IV) at

diagnosis [4]. The poor prognosis of locally advanced HNSCC has been noted after conventional surgical and radiation treatments, with only 30–50% of patients surviving for 3 years [5]. On the other hand, chemoradiotherapy (radiotherapy plus concurrent chemotherapy; CRT) has become the standard for patients with unresectable disease [6] and for organ preservation [7, 8]. Incorporation of induction chemotherapy (i.e., chemotherapy as the initial treatment; ICT) into multi-modality management has been evaluated for more than two decades in advanced HNSCC, and has been shown to provide survival benefits in locally advanced cases [5, 9–12]. However, the result from meta-analysis only showed a small benefit in survival [13]. Therefore, the optimal strategy for the management of advanced HNSCC and the suitability of incorporation of induction chemotherapy into multi-modality treatment remains to be determined.

5-fluorouracil (5-FU) is still one of the most widely used agents in the first-line therapy of HNSCC. However, the limited therapeutic response in advanced HNSCC encouraged clinicians to modify the schedule of 5-FU administration. Pharmacokinetic modulating chemotherapy (PMC), which was designed to boost high serum 5-FU concentrations through modulation by tegafur–uracil (UFT or UFUR®), consists of a continuous intravenous infusion of 5-FU over 24 h for 1 day and an oral dose of tegafur–uracil for 5–7 days per week [14]. The UFT or UFUR® is a combination of tegafur, a prodrug of 5-FU, and uracil at a molar ratio of 1:4 [14]. Dihydropyrimidine dehydrogenase (DPD), a key enzyme in the degradation of 5-FU into therapeutically inactive metabolites, catalyzes the reduction of 60–90% of administered 5-FU, and its catalytic activity correlates with the rate of 5-FU clearance [15]. Uracil inhibits hepatic DPD and thus enhances the plasma 5-FU level and the antitumor activity of 5-FU [16]. Previous study demonstrated that the PMC regimen maintained the 5-FU concentration above 200 ng/ml for 20 h [17], which was significantly higher than the non-PMC regimen in another study of the same group [18]. Further in vitro study showed that 5-FU acted via two different dosage depending pathways: one was G_1-S-phase with cell cycle arrest and apoptosis at 1,000 ng/ml, and the other one was G_2-M-phase with cell cycle arrest and mitotic catastrophe at 100 ng/ml. This suggested that the dual antitumor effect of PMC was based on targeting at least two different phases of cell cycles through different concentration of 5-FU [17]. The therapeutic efficacy of PMC has been demonstrated in metastatic colorectal cancers, with superiority to non-PMC 5-FU infusion [18].

Regarding the combination chemotherapy in HNSCC, the combination of 5-FU and cisplatin (the CF regimen) is one of the most commonly used regimens in advanced HNSCC, both in the induction and recurrent settings [5, 11, 12, 19, 20]. In order to improve the response rate to the traditional CF regimen in HNSCC, we incorporated cisplatin into PMC (i.e., the PMC-cisplatin protocol) as the induction chemotherapy. The aim of this phase II study was to evaluate the treatment response and tolerability of PMC-cisplatin as the induction chemotherapy before definitive treatment in advanced HNSCC. The organ preservation rate, overall survival (OS) and disease-free survival (DFS) were also evaluated in patients receiving completed course of multimodality treatment.

Materials and methods

Study design

This is a phase II study. Our aim was to evaluate the effectiveness and tolerability of PMC-cisplatin as induction chemotherapy (ICT) in resectable locally advanced HNSCC patients for organ preservation intent. The organ preservation rate and survival of the patients receiving completed course of multimodality treatment (i.e., induction chemotherapy follows by definitive CRT or surgery) will also be evaluated. The primary end point was the assessment of the efficacy in terms of treatment response and toxicity of PMC-cisplatin as ICT. To investigate the effectiveness of the multimodality treatment, the overall (OS) and disease-free survival (DFS) after ICT/CRT or ICT/surgery were also assessed as secondary end points. The sample size was calculated based on the two-stage design by Simon [21]. The treatment program was designed to refuse response rates of 60% (P0) and to provide a significance level of 0.05 (α) with a statistical power of 80% ($\beta = 0.2$) in assessing the activity of the regimen as an 80% response rate (P1). Thus, the first step was planned to include 11 patients; if >7 patients' responses were recorded, the study would enroll an additional 32 patients up to a total number of 43 patients. The regimen would be considered active if >30 responses were recorded. The approval of the local ethics committee was obtained before the start of the trial.

Eligibility

Patients with histologically documented stage III–IV locally advanced resectable, non-nasopharyngeal and treatment naïve HNSCC were enrolled. Only cases with radiological evidence of measurable (>2 cm) lesions were eligible for the study. Further entry criteria were: age 18–75 years, Karnofsky performance status ≥60, life expectancy >3 months, absolute neutrophil count (ANC) ≥1,500/μl, platelet count (PLT) ≥150,000/μl, creatinine clearance (CCR, estimated by Cockroft-Gault Formula) ≥50 ml/min, total bilirubin within normal range. Before

study entry, all patients were required to provide a written informed consent to the protocol.

Exclusion criteria were: unresectable disease according to Adelstein criteria including extensive primary tumors which are impossible for resection or functional reconstruction; metastatic cervical lymph nodes fixed to the carotid artery, the mastoid, the base of skull, or the cervical spine [6]. The unresectability was evaluated and confirmed by a multidiscipline treatment team including otolaryngologist, radiation oncologist, medical oncologist, radiologist and pathologist. Other exclusion criteria included previous or concurrent malignancies at other sites, uncontrolled severe infection and/or medical problems unrelated to malignancy that would limit full compliance with the study or expose the patient to extreme risk.

Treatment plan

Pretreatment workup

Within 14 days of the beginning of the study treatment, patients were submitted to a complete evaluation including computed tomography scan or magnetic resonance imaging of the head and neck region, endoscopy, chest X-ray, abdominal sonography, and laboratory tests including complete blood cell count, serum chemistry, and urinalysis.

Induction chemotherapy

The PMC was administered with tegafur–uracil (UFUR®, TTY Biopharm, Taipei, Taiwan) 250 mg/m^2/day orally from day 1 to day 5, leucovorin 250 mg/m^2 i.v. infusion for 2 h on day 1 and 5-FU 600 mg/m^2 continuous i.v. infusion for 24 h on day 1. Cycles were repeated every week up to a total of 6 cycles. It was combined with cisplatin 100 mg/m^2 continuous i.v. infusion for 24 h on day 1 of cycles 1 and 4.

Definitive treatment after induction chemotherapy

After patients completed six cycles of induction chemotherapy, the evaluation of response was performed by the radiologist and otolaryngologist. We allocated the responders (complete or partial response) of ICT to receive subsequent CRT and non-responders (stable or progressive disease) to receive salvage surgery. The ICT responders would receive CRT with cisplatin 30 mg/m^2 i.v. infusion for 2 h on day 1 and oral tegafur–uracil (UFUR®) 250 mg/m^2/day on days 1–5 repeated every week, combined with external beam radiotherapy 70 Gy for primary tumor and clinical positive nodes, and 50 Gy for areas at risk of microscopic disease for a total of 7 weeks. If there was still residual disease after CRT, salvage surgery would be performed because further chemotherapy or radiotherapy is not suitable in this scenario, and surgery is indicated to treat the residual cancer after CRT [12, 22]. Non-responders would receive salvage surgery and postoperative CRT (cisplatin 30 mg/m^2 on day 1 and tegafur–uracil 250 mg/m^2/day on days 1–5 repeated every week, combined with radiotherapy 66 Gy for high-risk area and 54 Gy for all risk area for a total of 6 weeks). The treatment algorithm and schema are shown as Figs. 1 and 2.

Dose modification

In cases of hemoglobin <9 g/dl, ANC <1,000/μl and/or PLT <100,000/μl, treatment was postponed by 1 week. For patients who had delayed treatment for >2 weeks and in cases of development of hypersensitivity reactions, treatment was discontinued. If ANC <500/μl or PLT <50,000/μl for >5 days, cisplatin and 5-FU doses were reduced by 20% in the next cycle. If CCR decreased to 40–50 ml/min, cisplatin was reduced to 50% in the next cycle. If CCR <40 ml/min, treatment was withheld.

Response and toxicity assessment

Tumor responses were evaluated with the use of RECIST criteria [23]. Evaluation of the response to induction chemotherapy was performed on the first day of the seventh week, whereas the evaluation of response to CRT was

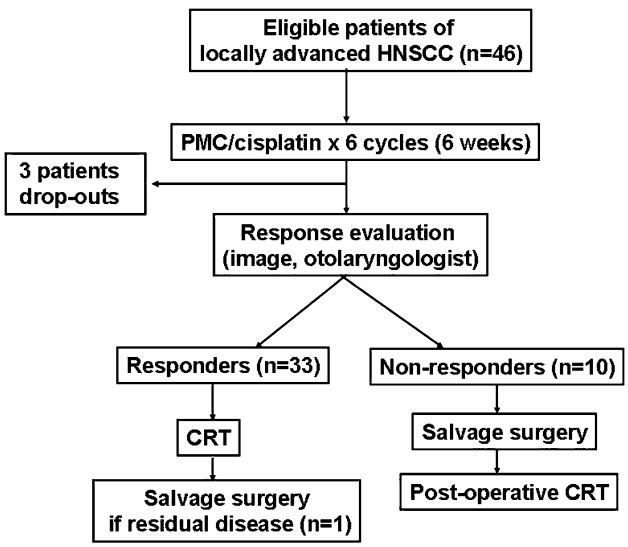

Fig. 1 Algorithm of PMC-cisplatin containing multimodality treatment. All eligible patients (n = 46) received PMC as induction therapy and 43 patients completed with a total of 6 cycles. The ICT responders (n = 33) received CRT. Salvage surgery was given only if there was residual disease after completion of treatment (n = 1). The ICT non-responders (n = 10) received immediate salvage surgery and postoperative CRT. *HNSCC* head and neck squamous cell carcinoma, *PMC* pharmacokinetic modulating chemotherapy, *ICT* induction chemotherapy, *CRT* concurrent chemoradiotherapy

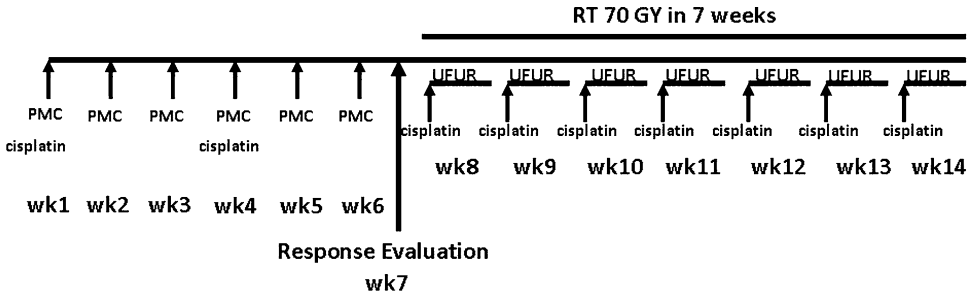

Fig. 2 Schema of PMC-cisplatin containing multimodality treatment. *PMC* pharmacokinetic modulating chemotherapy, *wk* week, *RT* radiotherapy

performed 2 months after completion of treatment and confirmed by images (CT or MRI) and endoscopy performed by otolaryngologists. The toxicity was graded according to the National Cancer Institute's Common Toxicity Criteria [24].

Statistical analysis

All analyses were accomplished by SPSS 14.0 (SPSS, Inc., Chicago, IL, USA). OS was defined as time elapsed between start of induction treatment and date of death or the date last seen. DFS was defined as time between complete remission (CR) achieved either after induction chemotherapy, CRT, or salvage surgery and date of recurrence or last follow-up. Median and life tables were computed using the product-limit estimate by the Kaplan–Meier method, and the log-rank test was applied for comparison of survival periods between groups. The response analysis of each clinical factor was compared making use of χ^2 or Fisher's exact test for category variables. Two-sided *P* values less than 0.05 were considered statistically significant.

Results

Patient characteristics

From March 2003 to August 2005, 46 patients (the intent-to-treat group, ITT) with stage III–IV non-nasopharyngeal, treatment naïve HNSCC were enrolled into this phase II trial. Three patients were lost to follow-up after induction chemotherapy: two cases were due to the intolerance of treatment, and the other one was due to the refusal of subsequent CRT. Finally 43 patients (the evaluable patients, EP) were analyzed as required. Regarding the characteristics of EPs, there were 39 men and 4 women included. At initial diagnosis, median age was 53 years (range 36–75 years). The primary sites included the oral cavity 25.6%, oropharynx 25.6%, hypopharynx 30.2%, larynx 7.0% and other sites (one cases with tumor originated from lip, two from nasal cavity, and two from paranasal sinuses) 11.6%. The demographics of the ITT and EP are detailed in Table 1.

Table 1 Baseline characteristics of patients

Variables	ITT[a] (%) (n^b = 46)	EP[c] (%) (n^b = 43)
Gender		
Male	42 (91.3)	39 (90.7)
Female	4 (8.7)	4 (9.3)
Age		
Range (years)	36–75	36–75
Median (years)	53	53
<50	16 (34.8)	15 (34.9)
≥50	30 (65.2)	28 (65.1)
Smoking		
Yes	36 (78.3)	33 (76.7)
No	10 (21.7)	10 (23.3)
Alcohol drinking		
Yes	32 (69.6)	31 (72.1)
No	14 (30.4)	12 (27.9)
Betel nut chewing		
Yes	30 (65.2)	29 (67.4)
No	16 (34.8)	14 (32.6)
Primary site		
Oral cavity	12 (26.2)	11 (25.6)
Oropharynx	13 (28.3)	11 (25.6)
Hypopharynx	13 (28.3)	13 (30.2)
Larynx	3 (6.5)	3 (7.0)
Other sites	5 (10.7)	5 (11.6)
T stage		
2	14 (30.4)	12 (27.9)
3	17 (37.0)	16 (37.2)
4	15 (32.6)	15 (34.9)
N stage		
0	8 (17.4)	8 (18.6)
1	5 (10.9)	4 (9.3)
2	30 (65.2)	28 (65.1)
3	3 (6.5)	3 (7.0)
TNM		
III	13 (28.3)	13 (30.2)
IV	33 (71.7)	30 (69.8)

[a] Intent-to-treat population

[b] Number of patients

[c] Evaluable population

Results of induction chemotherapy and definitive treatment

After 6 cycles of PMC-cisplatin induction chemotherapy, all patients were available for response evaluation. In the 46 ITT cases, 11 (24%) complete remission (CR) and 25 (54%) partial response were registered, with an overall response rate (RR) of 78%. The ICT results of the 43 evaluable patients are: 10 (23%) with CR, 23 (54%) with PR, and overall RR was 77%. The treatment result of ICT is summarized in Table 2.

After induction chemotherapy, the responders of the EP group (33 cases, 76%) were assigned to receive subsequent CRT, and the salvage surgery was performed in the non-responders (10 cases, 24%) according to the treatment algorithm. Regarding the ICT responders, all 33 cases received complete course of CRT with delayed completion of CRT in 6 (18.2%) cases. The most important cause of delayed completion of CRT was severe mucositis (≥grade III mucositis was noted in five of six cases with delayed completion). Thirty-two out of 33 (97%) CRT cases achieved CR after treatment, and only one case was found to have residual disease two months after completion of CRT. Salvage surgery was performed in this case with the rationale described in the section of Methods. The ICT non-responders included four patients (9%) with stable disease and 6 patients (14%) with progressive disease. Salvage surgery was performed immediately and postoperative adjuvant CRT was given after recovery from surgery. The overall organ preservation rate for EP group in this study was 75%. However, an excellent organ preservation result was demonstrated in the ICT responder group (32 of 33 patients, 97%). The overall treatment profile and results are illustrated in the algorithm (Fig. 1).

Table 2 Treatment response of PMC-cisplatin as induction chemotherapy

Response	ITT[e] (n[f])	%	EP[g] (n[f])	%
CR[a]	11	24	10	23
PR[b]	25	54	23	54
SD[c]	4	9	4	9
PD[d]	6	13	6	14

PMC Pharmacokinetic modulating chemotherapy

[a] Complete remission

[b] Partial response

[c] Stable disease

[d] Progressive disease

[e] Intent-to-treatment population

[f] Number of patients

[g] Evaluable population

Survival analysis

Follow-up data were available for all 43 evaluable patients. As of December 2007, median follow-up duration was 25 months (range 5–50 months). A total of 47% of patients were still alive with CR. The 3-year OS rate was 67% and the DFS was 39% (Fig. 3).

Toxicity

The toxicity profile of PMC-cisplatin is shown in Table 3. No treatment-related deaths or grade 4 toxicity occurred among the common side effects. The percentage of all grade 3 events was 26%. As far as hematological toxicity was concerned, grade 3 neutropenia affected 6 (13%) patients. No grade 3 anemia was noted in all cases and grade 3 thrombocytopenia only occurred in two (4%) patient. Regarding non-hematological toxicity, the most common side effect was oral mucositis; 33 (71.7%) patients suffered from this adverse effect and grade 3 mucositis developed in 4 (9%) patients. There were 2 (4%) patients with grade 2

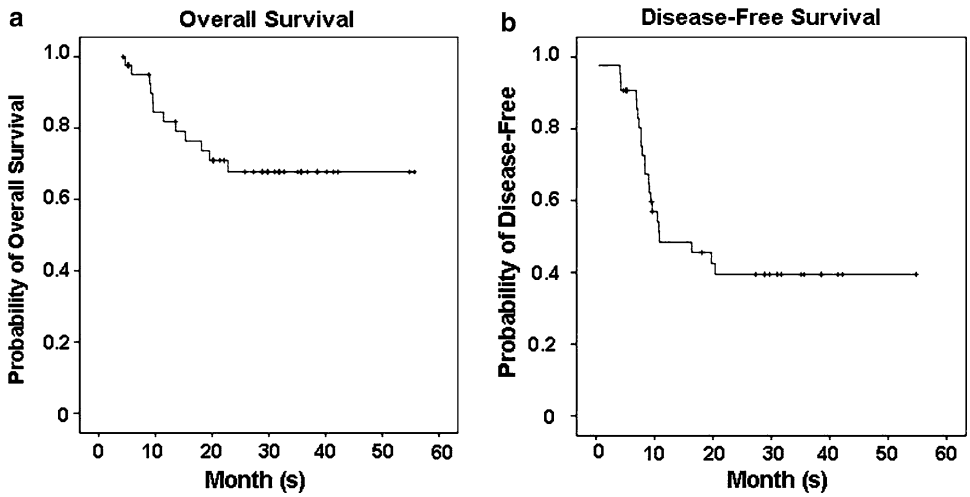

Fig. 3 Kaplan–Meier survival curves of overall survival (**a**) and disease-free survival (**b**) for 43 locally advanced head and neck cancer patients receiving PMC-cisplatin containing multimodality treatment. *PMC* pharmacokinetic modulating induction chemotherapy

Table 3 Toxicity profile of PMC-cisplatin as induction chemotherapy

Toxicity	ITT[b] ($n = 46$)							
Grade	1		2		3		4[a]	
Numbers (%)	n	%	n	%	n	%	n	%
Hematologic								
Anemia	21	46	6	13	0	0	0	0
Neutropenia	10	22	10	22	6	13	0	0
Thrombocytopenia	7	15	1	2	2	4	0	0
Infection	2	4	0	0	0	0	0	0
Nephropathy	5	11	2	4	0	0	0	0
Neuropathy	0	0	0	0	0	0	0	0
Hepatotoxicity	1	2	0	0	0	0	0	0
Oral mucositis	14	30	15	33	4	9	0	0
Nausea/Vomiting	6	13	1	2	0	0	0	0
Diarrhea	1	2	0	0	0	0	0	0

PMC Pharmacokinetic modulating chemotherapy

[a] No grade 4 toxicity was seen

[b] Intent-to-treatment population

Table 4 Toxicity profile of CRT after induction chemotherapy ($n = 33$)

Toxicity	Grade[a]							
	1		2		3		4	
	N	%	N	%	N	%	N	%
Hematologic								
Anemia	16	50	6	20	2	6	1	3
Neutropenia	9	27	8	24	6	18	0	0
Thrombocytopenia	7	21	6	20	1	3	0	0
Infection	1	3	1	3	3	9	0	0
Nephropathy	2	6	2	6	1	3	0	0
Neuropathy	2	6	1	3	0	0	0	0
Hepatotoxicity	1	3	0	0	0	0	0	0
Oral mucositis	10	30	15	45	6	18	0	0
Nausea/Vomiting	5	12	9	27	0	0	0	0
Diarrhea	2	6	5	15	2	6	0	0
Dysphagia/Esophagitis	13	39	8	24	5	15	0	0
Anorexia	15	45	10	30	5	15	3	9
Body weight loss	10	30	6	18	0	0	0	0

CRT Concurrent chemoradiotherapy

[a] Chemotherapy was postponed for 1 week in patients with grade 3 or grade 4 hematologic toxicity, infection or nephropathy. CRT was hold only if grade 4 neutropenia developed, or other adverse events compromised patients' performance severely (e.g., severe mucositis)

nephrotoxicity and one (2%) patient with grade 2 nausea/vomiting. In general, the PMC-cisplatin regimen was well tolerated. The adverse effects were transient and no severe treatment-related morbidity/mortality was reported in our study. Regarding the toxicity of definitive CRT of 33 cases, one patient had grade 4 anemia (3%) and 3 patients (9%) had grade 4 anorexia. Other common grade 3 toxicity included neutropenia (18%), oral mucositis (18%), dysphagia/esophagitis (15%), and anorexia (15%). The details of CRT toxicity are shown in Table 4.

Discussion

The PMC regimen was first proposed to show that incorporation of oral tegafur–uracil would enhance both plasma 5-FU concentrations (fivefold) and antitumor effects (twofold) compared with 5-FU infusion alone [14]. The special biochemical modulation and chronomodulation induced by orally administered tegafur–uracil during continuous infusion of 5-FU also improved the therapeutic response in colorectal carcinoma independent of p53 status, which was one of the major determinants of 5-FU responsiveness [25, 26], both in vitro [17] and in vivo [27]. Concerned about the high frequency of p53 polymorphism associated with HNSCC [28, 29] and CF as the standard treatment for HNSCC patients, we designed this regimen to combine cisplatin and PMC as induction chemotherapy with cumulative dose similar to previous studies [30, 31]. The pilot study of PMC-cisplatin as induction therapy was performed in ten advanced HNSCC patients and showed a promising result (data not shown). The good response and acceptable toxic profile of PMC-cisplatin encouraged us to perform this phase II study, and it has shown consistent and promising results: a high response rate with acceptable safety profile of PMC-cisplatin as induction chemotherapy was demonstrated in the locally advanced HNSCC cases. In addition, the organ preservation rate, 3-year OS and DFS of this combined modality treatment (ICT-CRT or ICT-surgery) is also promising. As far as we know, this is the first study demonstrating the benefit of the PMC-cisplatin regimen as induction chemotherapy in locally advanced HNSCC.

Induction chemotherapy has been one of the most important issues in the management of locally advanced HNSCC patients over the last 30 years. This therapeutic modality has been used in strategies aiming at organ preservation as well as the survival benefit of patients with advanced HNSCC [5, 11, 32, 33]. The CF regimen has been considered as the standard treatment of induction chemotherapy of advanced HNSCC [34, 35]. Recent studies have demonstrated a further improvement of treatment outcome by incorporating taxanes (paclitaxel, docetaxel) into CF regimen as induction therapy of HNSCC [5, 11, 12, 19]. The survival benefit has also been observed in docetaxel-CF compared with CF alone (3-year OS 62% in docetaxel-CF vs. 48% in CF group [19]). Though not under parallel

conditions, considering the higher ratio of poor prognostic patients (72.1% ≥ N2 and 30.2% hypopharynx cancer) in our study, our results demonstrate a promising overall induction response rate (76%) and 3-year OS rate (67%), which is superior to traditional CF used as induction chemotherapy (3-year OS 30–50%) [5, 11, 12]. These results suggest that further randomized phase III studies are warranted to confirm the superiority PMC-cisplatin compared with traditional CF in HNSCC. Incorporation of taxanes into PMC-cisplatin regimen also deserves further study.

Although several reports have shown the benefits, the role of induction chemotherapy before CRT has yet to be determined [11, 12, 19, 36]. The rationale of adding ICT before CRT is that induction chemotherapy reduces the tumor bulk, improves oxygenation and might lead to vascular improvement, which leads to an improvement of response to radiotherapy [13]. Furthermore, induction chemotherapy could be regarded as an indicator of the responsiveness to subsequent CRT, and surgery could be applied earlier in cases of poor response to induction chemotherapy to prevent unnecessary CRT [12, 13, 22]. However, the data evaluating the role of induction chemotherapy before definite CRT is still very limited. We therefore aimed to investigate the role of adding effective induction therapy before CRT in advanced HNSCC. The results showed that there was a very high organ preservation rate (97%) in the PMC-cisplatin responders, which indicated the effectiveness of PMC-cisplatin before CRT. Regarding the length of induction chemotherapy, a previous report suggested that extended treatment courses of induction chemotherapy might induce accelerated repopulation of surviving tumor clonogens and increase toxicity [37]. In our study, after 6 weeks of PMC-cisplatin induction chemotherapy, the responsive patients showed better long-term DFS compared to the non-responders (Fig. 4, median survival 20.4 vs. 9.0 months, $P = 0.02$), while there was no significant difference of OS between these two groups (median survival not reached vs. 19.5 months, $P = 0.09$, data not shown). This result implied that tumors primarily refractory to induction chemotherapy had higher early recurrence rates. Shortening the induction chemotherapy course to 6 weeks could provide earlier selection of primary chemo-refractory patients to receive salvage surgery and avoid unnecessary CRT, which might result in reduced toxicity, better loco-regional control and prolonged OS. Further large-scale studies are warranted to confirm this observation.

Regarding the selection of chemotherapeutic regimen during CRT, previous studies have shown the efficacy and reduced toxicity of weekly cisplatin with doses ranging from 30 to 40 mg/m^2 in upper-aerodigestive squamous cell carcinoma [38–41]. The benefit of using tegafur–uracil during CRT has also been demonstrated [42, 43]. We therefore designed the CRT protocol using separated doses of cisplatin combined with tegafur–uracil to test its effectiveness and safety as an out-patient regimen, and it showed a promising result (97% CR and 3% PR in 33 responders of ICT) with acceptable toxicity (Table 4).

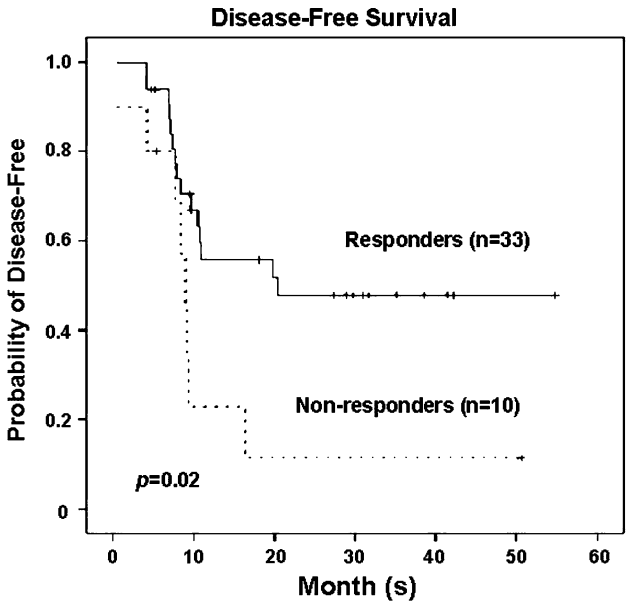

Fig. 4 Kaplan–Meier disease-free survival curves of IC responders versus non-responders of 43 locally advanced head and neck cancer patients receiving PMC-cisplatin containing multimodality treatment. *PMC* pharmacokinetic modulating chemotherapy, *IC* induction chemotherapy

In conclusion, the PMC-cisplatin induction chemotherapy provides a high treatment response rate and acceptable safety profile in resectable locally advanced HNSCC. The organ preservation rate and survival result of the combined modality therapy (ICT-CRT or ICT-surgery) is also promising. These results suggest the further studies to investigate the probability of using PMC-cisplatin in replacement of traditional CF regimen as ICT in advanced HNSCC, and incorporation of taxane or new targeting agents into PMC-cisplatin as ICT warrants further evaluation.

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