The Journal of Laryngology & Otology (2008), ***122***, *848–853.*

doi:10.1017/S0022215107001181

Main Article

Induction chemotherapy with S-1 plus cisplatin in patients with locally advanced squamous cell carcinoma of the head and neck

Y J Choi, J S Chung, H-J Shin, G J Cho, S G Wang*, B J Lee*, B M Cho†, Y D Joo‡, C H Sohn‡

Abstract

Objective: This study was performed to assess the efficacy and safety profile of combination treatment with S-1 and cisplatin in patients with locally advanced squamous cell carcinoma of the head and neck.

Design: Eligibility criteria comprised: histologically confirmed squamous cell carcinoma of the head and neck; stage three or four disease with no evidence of distant metastasis; evaluable lesions; adequate organ function; age 20–80 years; and a performance status of two or less. Cisplatin was infused over one hour on day one (75 mg/m^2) and S-1 was administered orally for 14 consecutive days (days two to 15). The dosages of S-1 were calculated according to the patients' body surface area: 50 mg twice a day (body surface area <1.5 m^2) or 60 mg twice a day (body surface area >1.5 m^2). Each course was repeated every three weeks. After two courses, tumour response was evaluated by computed tomography and laryngoscopy. If a response was evident (either complete or partial), the patient received one more course of chemotherapy, before undergoing radical treatment such as radiotherapy or surgery.

Results: All 30 patients were assessable for toxicity, and 29 patients for treatment response. The overall response was 89.7 per cent (complete response: nine; partial response: 17). The two-year estimated overall survival rate was 79.2 per cent. Adverse reactions occurred 128 times during 81 courses in the 30 cases. The most common grade three to four adverse event was neutropenia, which occurred in eight patients. Cases of non-haematological grade three or four toxicity included nausea and vomiting in four patients, stomatitis in two and diarrhoea in one.

Conclusion: S-1 plus cisplatin combination chemotherapy is effective against locally advanced squamous cell carcinoma of the head and neck, with only mild toxicity.

Key words: Head and Neck Neoplasms; Anti-Neoplastic Agents; Cisplatin; Toxicity

Introduction

Squamous cell carcinoma (SCC) of the head and neck is a potentially curable malignancy when diagnosed at an early stage. However, the majority of patients with head and neck SCC present with locally advanced disease, and the prognosis has remained poor in this group. Approximately 50–60 per cent of patients have local disease recurrence within two years, and 20–30 per cent of patients develop distant metastatic disease.[1,2] In an effort to improve treatment outcomes for locally advanced head and neck SCC, chemotherapy has been integrated into combined modality approaches involving surgery, radiotherapy or both.

In two meta-analytical studies of chemotherapy for head and neck cancer, concurrent chemoradiotherapy was found to have significant effects, providing an 8 per cent absolute survival benefit at five years.[3] However, concurrent chemoradiotherapy entails increased toxicity, such as mucositis and dermatitis.

Induction chemotherapy yields four advantageous outcomes: primary organ preservation,[4–6] improved locoregional control,[4–6] reduced distant failure[4–6] and improved survival.[3,7–9] Induction chemotherapy with 5-FU and cisplatin (PF) (100 mg/m^2 cisplatin on day one and 1000 mg/m^2 5-fluorouracil (5-FU) by continuous infusion on days one to five) has become a standard regimen for patients with locally advanced head and neck cancer, providing overall response rates of 60–80 per cent.[10,11]

High response rates with docetaxel, cisplatin and 5-FU induction chemotherapy have also been seen in studies conducted in Europe and Japan, with overall response rates of 64–94 per cent, but grade three to four neutropenia has been a common serious adverse event.[12–15]

From the Departments of Hemato-oncology, *Otolaryngology and †Preventive Medicine, Pusan National University Hospital, and the Department of ‡Hemato-oncology, Inje University Hospital, Busan, Republic of Korea.
Accepted for publication: 4 September 2007. First published online 30 November 2007.

Since oral agents have the advantage of greater convenience and compliance, we planned a new, oral administration based regimen which could be carried out safely and which would have equivalent antitumour activity to previous regimens. We therefore selected a combination of S-1 and cisplatin.

Of the various oral anticancer agents available for the treatment of unresectable, advanced carcinomas, the dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine known as S-1 (Taiho Pharmaceutical, Tokyo, Japan) has shown the highest response rate in phase II studies.[16] S-1 is an oral anticancer agent consisting of tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate (Oxo), at a molar ratio of 1:0.4:1.[16,17] Tegafur is a prodrug of 5-FU, and 5-chloro-2,4-dihydroxypyridine enhances the serum 5-FU concentration by competitive inhibition of dihydropyrimidine dehydrogenase. Potassium oxonate is a reversible, competitive inhibitor of orotate phosphoribosyl transferase and inhibits phosphorylation of 5-FU in the gastrointestinal tissue, reducing the diarrhoea associated with 5-FU.[18] S-1 can maintain therapeutic plasma 5-FU concentration by inhibiting dihydropyrimidine dehydrogenase activity, while also reducing the gastrointestinal adverse reactions which contribute to one of the dose-limiting toxicities of 5-FU. In a phase II trial of advanced and recurrent head and neck SCC, S-1 showed a high response rate of 28.8 per cent, with acceptable toxicities.[19] In a preclinical study, S-1 has also shown synergistic effects with cisplatin.

Here, we describe our findings regarding the antitumour activity and safety profile of S-1 plus ciplastin treatment for locally advanced head and neck SCC.

Materials and methods

Patients

The following eligibility criteria were used: histologically or cytologically confirmed head and neck SCC; stage three or four disease with no evidence of distant metastasis; primary tumour located in the nasopharynx, oropharynx, hypopharynx, larynx or oral cavity; evaluable lesion; adequate organ function; age 20–80 years; Eastern Cooperative Oncology Group performance status zero, one or two; WBC count 4000 mm^{-3} or more; absolute neutrophil count 2000 mm^{-3} or more; platelet count 100 000 mm^{-3} or more, haemoglobin level 9.5 g/dl or more; aspartate transaminase, alanine transaminase and alkaline phosphatase levels below 2.5 times the upper limit of normal; total bilirubin and creatinine levels below 1.5 times the upper limit of normal; blood urea nitrogen level below the upper limit of normal; and 24-hour creatinine clearance rate more than 60 ml/min. The exclusion criteria were: previous chemotherapy, radiotherapy or surgery; concomitant malignancy; significant heart failure; active infection; and active neurological or psychiatric disorders. The disease was defined as per American Joint Committee on Cancer criteria.

The study was approved and reviewed by our institutional review board, and a written statement of informed consent was obtained from each patient.

Treatment schedule

An intravenous injection of cisplatin (75 mg/m^2) was given over a one-hour period on day one, and S-1 was administered orally for 14 consecutive days (days two to 15). The dosages of S-1 were determined according to the patient's body surface area, as either 50 mg twice a day (body surface area $<1.5\ m^2$) or 60 mg twice a day (body surface area $>1.5\ m^2$). Each course was repeated every three weeks. After two courses, response was evaluated by computed tomography (CT) and laryngoscopy. If a response was evident (either complete or partial), the patient received one more course of chemotherapy before undergoing radiotherapy or surgery as a radical local treatment. Radiation therapy was started within four weeks of the last cycle of chemotherapy and was administered five days per week. It was given in daily fractions of 1.8 Gy, and the total dose to the primary tumour site was 70.2 Gy.

Response assessment

Patients were assessed for clinical response before the start of the third cycle. The clinical response was assessed for each patient, based on the result of physical examination, CT and laryngoscopy. A complete response was defined as the complete disappearance of all measurable and assessable lesions for at least four weeks. A partial response was defined as a reduction of 50 per cent or more in the sum of the products of the longest dimensions of measurable lesions, for at least four weeks. Stable disease was defined as the failure to observe a partial or complete response. Progressive disease was defined as a 25 per cent or more increase in the sum of the products of the longest dimensions of measurable disease, or the appearance of new lesions.

Efficacy was assessed after at least two cycles of chemotherapy. Toxicity was graded according to the common toxicity criteria (version 2.0) of the National Cancer Institute (US).

Statistical analysis

The primary endpoint was the overall tumour response rate after induction chemotherapy. The secondary endpoint was toxicity evaluation and analysis of response rate according to site, stage and nodal status. The sample size was planned on an expected response rate of 80 per cent, with an allowable error of 15 per cent and with a 95 per cent confidence interval. The required number of patients was 28. All patients who received at least two cycles of treatment were assessable for response. The chi-square test was used for comparisons of results. The significance level was defined as $p \leq 0.05$.

Results

Patient characteristics

We enrolled 30 patients with stage three and four head and neck SCC, from January 2005 to February

https://doi.org/10.1017/S0022215107001181 Published online by Cambridge University Press

2006. The median age was 60 years (range 43–78). The baseline characteristics of the study population are summarised in Table I. The primary tumour sites were as follows: larynx in 14 patients (47 per cent), hypopharynx in seven (23 per cent), oropharynx in six (20 per cent), oral cavity in one (3 per cent) and nasopharynx in two (7 per cent). The tumour and lymph node staging of all patients is listed in Table II. There were 13 patients (43.3 per cent) with stage three tumours and 17 (56.7 per cent) with stage four. Twelve of 16 patients had N_1/N_2 disease, and there were no N_3 cases. There were six T_4 primary tumours.

Efficacy

Response was assessable in 29 patients. One patient was unassessable because he received only one cycle due to poor compliance. A total of 81 courses were given: 22 patients (73 per cent) received three courses and seven (17 per cent) received two courses. Of the seven patients who received only two cycles of chemotherapy, three had progressive disease and stable disease, they received radiation therapy. Four patients did not reach the third chemotherapy cycle because of severe side effects.

The response rates, according to primary site, are presented in Table III. The overall response rate was 89.7 per cent. A complete response was achieved by nine patients (31 per cent) and a partial response by 17 (58.6 per cent). Stable disease and progressive disease were seen in one and two patients, respectively.

Of the 28 patients with nodal metastases, a complete response was achieved by eight (28.6 per cent) and a partial response by 18 (64.2 per cent). The complete response ratio of patients with N_0 or N_1 lesions was higher (42 per cent) than that of those with N_2 lesions (27 per cent), but this difference did not reach statistical significance ($p = 0.448$).

TABLE I

BASELINE PATIENT CHARACTERISTICS

Characteristic	*n* (%)
Patients	
Total	30 (100)
Assessable for response	30 (100)
Sex (M:F; *n*)	28:2
Age (yrs; median (range))	60 (43–78)
Primary tumour site	
Oropharynx	6 (20)
Hypopharynx	7 (23)
Larynx	14 (47)
Oral cavity	1 (3)
Nasopharynx	2 (7)
Performance status	
ECOG 0	2 (6.7)
ECOG 1	23 (76.7)
ECOG 2	5 (16.7)
Stage	
III	13 (43.3)
IV	17 (56.7)

M = male; F = female; yrs = years; ECOG = Eastern Cooperative Oncology Group

TABLE II

TUMOUR–NODE–METASTASIS STAGE*

Node stage	Tumour stage				Total
	T_1	T_2	T_3	T_4	
N_0	0	0	2	0	2
N_1	2	8	1	1	12
N_2	0	8	3	5	16
N_3	0	0	0	0	0
Total	2	16	6	6	30

*$n = 30$. Note that no patients with distant metastases were included in the study.

Response rates did not vary significantly according to site or stage. The median follow-up duration was 13 months. The one-year estimated time to treatment failure was 66 ± 10 per cent, and the two-year estimated overall survival was 79.2 ± 10.2 per cent (Figure 1).

Toxicity

All 30 patients were assessable for toxicity. Drug-related adverse events are listed in Table IV. A total of 81 cycles of chemotherapy were analysed. Five patients required a delay in scheduled chemotherapy, by a mean of one week, due to myelosuppression. Dose reduction of S-1 was necessary in three patients and dose reduction of cisplatin in five. The relative dose intensity was 0.985 for S-1 and 0.972 for cisplatin.

The main adverse events comprised haematological and gastrointestinal symptoms. There were no grade four adverse haematological events and no treatment-related deaths. Haematological toxicities comprised grade three neutropenia in eight patients and grade three anaemia in one. Stomatitis occurred in two patients (grade three in one and grade four in one). Severe diarrhoea occurred in one patient, and nausea and vomiting in three.

Discussion

Head and neck SCC makes up 5 per cent of new diagnoses of cancer, with more than 400 000 new cases annually worldwide. Although the condition is potentially curable with surgery or radiation in the early stages, relapses occur in 10–40 per cent of cases, and many are locally advanced on initial diagnosis.

Induction chemotherapy for head and neck SCC has been studied for more than three decades. Implementation of induction treatment is based on the anticipation of (1) better drug delivery to untreated tumour with preserved intratumoural vasculature; (2) reduction of tumour size, which could make surgery possible in cases of previously unresectable tumour, or could enable less extensive resection of resectable tumours; (3) early eradication of micrometastases; (4) higher doses and improved tolerance of cytotoxic drugs, with potentially more pronounced antitumour effect before irradiation; and (5) intermediate assessment of outcome, in order to guide planning of subsequent radiotherapy and surgery.[20,21]

https://doi.org/10.1017/S0022215107001181 Published online by Cambridge University Press

TABLE III

RESPONSE RATE ACCORDING TO PRIMARY SITE*

Disease site	Patients (*n*)	Response (*n* (%))			
		CR	PR	SD	Total
Oral cavity	1			1 (100)	
Oropharynx	6	2 (33.3)	3 (50)		5 (83.3)
Larynx	13	4 (30.8)	8 (61.5)		12 (92.3)
Hypopharynx	7	2 (28.6)	5 (71.4)		7 (100)
Nasopharynx	2	1 (50)	1 (50)		2 (100)
Total	29	9 (31)	17 (58.6)	1 (3.3)	26 (89.7)

*$n = 29$. CR = complete reponse; PR = partial response; SD = stable disease

The combination of 5-FU and cisplatin has been studied for more than three decades. Reported response rates have averaged 60–80 per cent, with complete responses in 20–30 per cent of patients. Recently, the addition of a taxane to standard platinum plus 5-FU has resulted in high response rates; the TAX 708 study, a phase I/II, multicentre study of combination treatment (docetaxel 75 mg/m^2, cisplatin 100 mg/m^2 and 5-FU 1000 mg/m^2/day for four days) yielded a 40 per cent complete response rate and a 93 per cent overall response rate, but accompanied by high rates of severe toxicity.[22] Combination treatment with 5-FU and cisplatin has caused mainly haematological toxicity, principally neutropenia, but nausea and vomiting, stomatitis, fatigue and other gastrointestinal toxicities have also occurred frequently.[12–15]

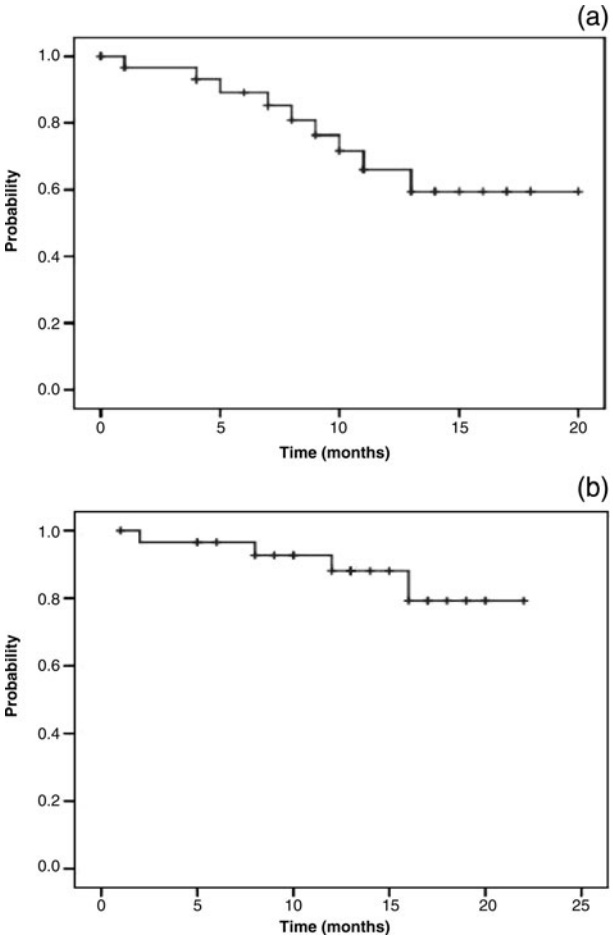

FIG. 1

(a) Time to progression and (b) overall survival for 29 patients with squamous cell carcinoma of the head and neck. For part (b), 2-year estimated overall survival = 79.2 ± 10.2 per cent.

S-1 is an oral anticancer agent consisting of tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate, at a molar ratio of 1 : 0.4 : 1. Tegafur itself is inactive, is absorbed very well after oral administration and has a long plasma half-life. Tegafur is gradually converted, primarily in the liver, by drug-metabolising P-450 enzymes into 5-FU, which has antitumour activity. Five-chloro-two, four-dihydroxypyridine strongly inhibits degradation of 5-FU released from tegafur, resulting in prolonged high concentrations of 5-FU in blood and tumour tissue, thereby enhancing antitumour activity. Potassium oxonate is an inhibitor of an enzyme for 5-FU anabolism; therefore, adverse gastrointestinal reactions caused by high levels of 5-FU, such as diarrhoea, are expected to be specifically reduced by potassium oxonate, without any decrease in antitumour activity.

The present study was designed to evaluate the activity and safety of oral S-1 and cisplatin combination chemotherapy in locally advanced head and neck SCC. The overall response rate observed in this study was 86.7 per cent, but complete response was 31 per cent. It is clear that patients who receive induction chemotherapy and who achieve a complete

TABLE IV

CHEMOTHERAPY TOXICITY*

Toxicity	Grade (*n*)			
	1	2	3	4
Leukopenia	14	6	2	0
Neutropenia	7	4	8	0
Thrombocytopenia	5	0	0	0
Anaemia	10	6	1	0
Nausea/vomiting	12	5	3	1
Creatinine elevation	2	0	0	0
Diarrhoea	3	1	0	1
Lethargy	2	2	1	0
Stomatitis	4	0	1	1
Anorexia	11	11	0	0
Alopecia	2	0	0	0
Neurotoxicity	4	0	0	0

*$n = 30$.

https://doi.org/10.1017/S0022215107001181 Published online by Cambridge University Press

pathological response have a better chance of responding to radiation therapy and hence have a better prognosis.[23]

- **This study was performed to assess the efficacy and safety profiles of combination treatment with S-1 and cisplatin in patients with locally advanced squamous cell carcinoma (SCC) of the head and neck**
- **The incidence of toxic effects were very low. There were no severe haematological events and no cases of neutropenic fever**
- **The most frequent adverse events were nausea and vomiting, stomatitis and diarrhoea**
- **A regimen of S-1 and cisplatin can be recommended to older patients with locally advanced head and neck SCC and to those with poor performance status**

In the present study, the incidence of toxic effects was very low. We observed no grade four haematological events and no neutropenic fever. The most frequent grade three to four adverse events were nausea and vomiting (four patients), stomatitis (two) and diarrhoea (one). In patients treated with docetaxel and cisplatin, treatment-related toxicity is a major concern; grade three to four neutropenia has been reported in 75 per cent of patients and febrile neutropenia in 17.1 per cent.[24,25]

Conclusion

Our S-1 and cisplatin regimen can be recommended to older patients with locally advanced head and neck SCC and those with poor performance status.

References

1 Forastiere AA, Koch W, Trotti A, Sidransky D. Medical progress: head and neck cancer. *N Engl J Med* 2001;**345**:1890–900
2 Posner MR, Haddad RI, Wirth L, Norris MR, Goguen LA, Mahadevan A *et al*. Induction chemotherapy in locally advanced squamous cell cancer of the head and neck: evolution of the sequential treatment approach. *Semin Oncol* 2004;**31**:778–85
3 Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet* 2000;**355**:949–55
4 Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collete L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. *J Natl Cancer Inst* 1996;**88**:890–8
5 Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrisson W *et al*. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* 2003;**349**:2091–8
6 Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med* 1991;**324**:1685–9
7 Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P *et al*. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced stage oropharynx carcinoma. *J Natl Cancer Inst* 1999;**91**:2081–6
8 Depondt J, Gehanno P, Martin M, Leievre G, Guerrier B, Peytral S *et al*. Neoadjuvant chemotherapy with carboplatin/5-fluorouracil in head and neck cancer. *Oncology* 1993;**50**:23–7
9 Domenge C, Hill C, Lefebvre JL, De Raucourt D, Rhein B, Wibault P *et al*. Randomized trial of neoadjuvant chemotherapy in oropharyngeal carcinoma. *Br J Cancer* 2000;**83**:1594–8
10 Monnerat C, Faivre S, Temam S, Bourhis J, Raymond E. End points for new agents in induction chemotherapy for locally advanced head and neck cancers. *Ann Oncol* 2002;**13**:995–1006
11 Rooney M, Kish J, Jacobs J, Kinzie J, Weaver A, Crissman J *et al*. Improved complete response rate and survival in advanced head and neck cancer after three-course induction therapy with 120-hour 5-FU infusion and cisplatin. *Cancer* 1985;**55**:1123–8
12 Janinis J, Papadakou M, Panagos G, Panousaki A, Georgoulias V, Hatzidaki D *et al*. Sequential chemoradiotherapy with docetaxel, cisplatin, and 5-fluorouracil in patients with locally advanced head and neck cancer. *Am J Clin Oncol* 2001;**24**:227–31
13 Schrijvers D, Van Herpen C, Kerger J, Joosens E, Van Laser C, Awada A *et al*. Docetaxel, cisplatin, and 5-fluorouracil in patients with locally advanced unresectable head and neck cancer: a phase I–II feasibility study. *Ann Oncol* 2004;**15**:638–45
14 Tsukuda M, Mikami Y, Tanigaki Y, Katori H, Horiuchi C, Ikeda Y *et al*. Phase I trial of combined chemotherapy with docetaxel, cisplatin, and 5-fluorouracil for patients with locally advanced squamous cell carcinoma of the head and neck. *Int J Clin Oncol* 2004;**9**:161–6
15 Watanabe A, Taniguchi M, Sasaki S. Induction chemotherapy with docetaxel, cisplatin, fluorouracil and 1-leucovorin for locally advanced head and neck cancer: a modified regimen for Japanese patients. *Anticancer Drugs* 2003;**14**:801–7
16 Schoffski P. The modulated oral fluropyrimidine prodrug S-1, and its use in gastrointestinal cancer and other solid tumors. *Anticancer Drugs* 2004;**15**:85–106
17 Shirasaka T, Nakano K, Takechi T, Satake H, Uchida J, Fujioka A *et al*. Antitumor activity of 1_Mtegafur-0.4_M 5-chloro-2,4dihydroxypyridine-1_Mpotassium oxonate (S-1) against human colon carcinoma orthotopically implanted into nude rats. *Cancer Res* 1996;**56**:2602–6
18 Shirasaka T, Shimamoto Y, Fukushima M. Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. *Cancer Res* 1993;**53**:4004–9
19 Inuyama Y, Kida A, Tsukuda M, Kohno N, Satake B. Late phase II study of S-1 in patients with advanced head and neck cancer [in Japanese]. *Gan To Kagaku Ryoho* 2001;**28**:1381–90
20 Perez A, Brady W. Chemoirradiation in head and neck cancer: a review – part I. *PRRO Updates* 2(2), 2001; Part II. Lippincott Williams and Wilkins PRRO updates 2(3), 2001
21 Posner MR, Colevas AD, Tishler RB. The role of induction chemotherapy in the curative treatment of squamous cell carcinoma of the head and neck. *Semin Oncol* 2000; **27**(suppl G):13–24
22 Posner MR, Glisson B, Frenette G, Al-Sarrat M, Colevas AD, Norris CM *et al*. A multi-center phase I–II trial of docetaxel, cisplatin, and fluorouracil induction chemotherapy for patients with locally advanced squamous cell cancer of the head and neck. *J Clin Oncol* 2001;**19**:1096–104
23 Spaulding B, Fischer G, Wolf T. Tumor response, toxicity, and survival after neoadjuvant organ-preserving chemotherapy for advanced laryngeal carcinoma. *J Clin Oncol* 1994;**12**:1592–9
24 Specht L, Larsen SK, Hansen HS. Phase II study of docetaxel and cisplatin in patients with recurrent or disseminated squamous-cell carcinoma of the head and neck. *Ann Oncol* 2000;**11**:845–9

25 Fonseca E, Grau JJ, Stastre J, Garcia-Gomez JM, Rueda A, Pastor M *et al.* Induction chemotherapy with cisplatin/docetaxel versus cisplatin/5-fluorouracil for locally advanced squamous cell carcinoma of the head and neck: a randomised phase II study. *Eur J Cancer* 2005;**41**:1254–60

Address for correspondence:
Professor Jooseop Chung,
Department of Hematology-oncology,
Pusan National University Hospital,
1-10 Ami-Dong, Seo-Gu,
Busan 602-739, South Korea.

Fax: 82 51 254 3127
E-mail: porori701@hanmail.net

Professor J Chung takes responsibility for the integrity of the content of the paper.
Competing interests: None declared

https://doi.org/10.1017/S0022215107001181 Published online by Cambridge University Press