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ORIGINAL ARTICLE

Paclitaxel, cisplatin and 5-fluorouracil in recurrent squamous cell carcinoma of the head and neck: A phase II trial from an Italian cooperative group

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Abstract

The aim of this multicenter trial was to test the feasibility and the activity of a three-drug combination where paclitaxel is added to cisplatin and 5-fluorouracil. Patients with metastatic or relapsed SCC-HN unsuitable for further loco-regional radical treatment, not previously treated with chemotherapy, were eligible to receive paclitaxel 160 mg/m2 (3-hr infusion) day 1, CDDP 25 mg/m2/day and 5-FU 250 mg/m2/day bolus on days 1, 2, 3 every three weeks up to a maximum of five courses. Fourty-seven patients were enrolled by five Institutions in Italy. Main grade III–IV toxicities were: neutropenia (48%), thrombocytopenia (6%), anemia (4%), diarrhea (2%), mucositis (2%). Six patients had a complete response (13.3%) and eight a partial response (17.8%). Median progression free survival and overall survival are 4.1 and 7.9 months. One-year progression free survival and overall survival are 16% and 29%. This three-drug regimen has an excellent safety profile. The activity in the palliation of recurrent SCC-HN, however, does not appear to be improved in comparison with cisplatin and 5-fluorouracil or cisplatin and paclitaxel regimens. Recent studies indicate a more promising role of taxanes including triplets in the induction therapy of previously untreated patients.

The combination of cisplatin and 5-fluorouracil has been the most active regimen in squamous-cell carcinoma of the head and neck during the last two decades. For this reason, it has been widely used as standard chemotherapy for patients with metastatic and/or relapsed head and neck cancer, despite the lack of a clear advantage in survival over single agent chemotherapy.

The phase II studies with cisplatin and continuous infusion of 5-fluorouracil published in the 1980's, reported a mean objective response rate of 50% (range: 11–71%) [1–5]. Unfortunately, these data were not confirmed in the randomized studies published between 1990 and 1994. In these trials the objective response rates observed with the same regimen ranged from 24% to 32% and the median survival was between 6 and 8 months [6–8].

A modified cisplatin/5-fluorouracil combination where cisplatin is given in five daily doses (20 mg/m2/day) and 5-fluorouracil as I.V. bolus for five consecutive days (200 mg/m2/day) was tested in our Institute almost two decades ago. In a phase II trial [9] this regimen showed an antitumoral activity comparable to the original so called "Al Sarraf regimen" in which 5-fluorouracil is given as a continuous 96-hours infusion and cisplatin as a single dose on day 1. Moreover our regimen showed less gastrointestinal and mucosal toxicity allowing out-patient administration, and a good tolerance when combined with radiation therapy [10]. For these reasons this schedule is still considered the standard chemotherapy in our Institute.

Paclitaxel is an active drug in head and neck squamous cell carcinoma. Also in this case, however,

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the very promising results obtained in phase II trials on recurrent disease employing this drug as a single agent [11] or in combination with cisplatin were not confirmed in randomized trials. In two phase III studies the combination of cisplatin and paclitaxel reached an overall response rate of 28% and 36% with a median survival of 7.3 and 9.0 months respectively [12,13]. Particularly, the latter study did not show any advantage of this combination over cisplatin and 5-fluorouracil neither in terms of activity or survival even if the taxane-containing doublet seems to have a better toxicity profile.

The inclusion of paclitaxel into a cisplatin/5-fluorouracil regimen may be a reasonable way to increase the activity. In a previous dose-finding trial from our group [14], the maximum tolerable dose of paclitaxel when combined with cisplatin (25 mg/m2/day) and 5-fluoruracil (250 mg/m2/day) both administered by i.v. bolus for three consecutive days, was 160 mg/m2. Here we report the results of the phase II study.

Materials and methods

Patients' selection

Patients included were between 18 and 75 years of age, had an Eastern Cooperative Oncology Group performance status of less than 3 and had to give their written informed consent approved by an ethical commitee. Patients enrolled were candidates for palliative therapy because of histologically, and/or radiologically proven loco-regional relapse and/or distant metastases of squamous cell carcinoma of the head and neck, and were unsuitable for effective salvage treatment.

Before the registration, patients were evaluated by physical examination, ENT examination and computed tomography scan or MNR. Blood sampling for safety laboratory (haematology and biochemistry) assessments were performed before start of chemotherapy.

Exclusion criteria included major cardiac impairments requiring continuous pharmacological support, severe hepatic dysfunction, and a prior history of cancer excluding skin basalioma. Patients who received prior chemotherapy, even in a front-line chemo-radiotherapy program, were excluded.

Treatment Plan

According to the results of the phase I study [14], patients were treated with paclitaxel 160 mg/m2 by 3-hour infusion on day 1, cisplatin 25 mg/m2/day from day 1 to 3 (total dose: 75 mg/m2) and 5-fluorouracil 250 mg/m2/day from day 1 to 3. Courses were repeated every three weeks. Cisplatin was given after a 45′ pre-hydration with 500 ml of saline containing KCl, 10 mEq, and before a 90′ post-hydration with 1 L of saline containing KCl, 10 mEq, and $MgSO_4$, 2 g. 5-fluorouracil was given as an i.v. bolus at the end of the post-hydration period. Patients had to receive at least two cycles of treatment. After re-evaluation of disease patients showing disease progression went off-study, those showing complete or partial response continued the treatment up to a maximum of five courses, those with stable disease continued up to a maximum of four courses.

Dexamethasone 20 mg i.v., clorfenamina 10 mg im. and ranitidine 100 mg i.v. were administered 30 minutes prior paclitaxel to minimize the chances of hypersensitivity reactions. Medication for emesis prophylaxis was not standardized in the protocol. A 5-HT3 antagonist was generally administered i.v. for patients who required emesis prophylaxis. The routine use of colony stimulating factors was not allowed.

Toxicity and response evaluation

Toxicity evaluation including physical examination, blood chemistry, renal and hepatic function, was carried out before each chemotherapy course. A blood cell count was also carried out weekly. In the case of severe haematological toxicity it was repeated every other day until recovery. Toxicity was evaluated according to the World Health Organization scale [15] and recorded as the worst grade experienced by patients during the treatment.

Response was evaluated after the second and the fourth course by physical examination, ENT examination and computed tomography scan or MNR and reported according to the Union International Contre le Cancer criteria [15].

Statistics

The study was an open-label, non-randomized, multicenter study. Five Institutions in Italy participated in the study. The primary endpoint was the response rate assessment. Secondary endpoints are safety, progression free survival and overall survival. The study was conducted according to the good clinical practice rules. The registration of the patients was centralized by sending a registration form to the Bristol-Myers Squibb (BMS) office in Rome. BMS also provided for monitoring protocol adherence and compliance and for data collection. Data were managed by an external agency.

The study treatment would be interesting for further investigations if an overall response rate of at least 40% was achieved. For a standard alpha

error of 0.05 and a beta error of 0.10, a two-step design was adopted [16]. In the first step 24 evaluable patients were to be enrolled. If at least 6 responses were demonstrated, 21 evaluable additional patients would be accrued, up to a total of 45 evaluable patients.

Actuarial survival and progression-free survival are calculated according to the Kaplan-Meier method [17]. All the patients are considered in these analyses. Patients dying without disease progression are considered to have progressive disease at the time of death.

Results

Fourty-seven patients entered the trial from January 1999 to December 2001. Details on patients' characteristics are given in Table I. All patients had recurrent and/or metastatic disease.

Six patients (13%) only had prior radiotherapy, 5 (11%) only prior surgery and 30 (64%) both. Six patients (13%) had no prior local treatment because they had metastatic disease at the time of the first diagnosis. Twenty-eight patients had loco-regional relapse (60%), 14 (30%) had loco-regional disease and distant metastases and five (10%) distant metastases only. Metastatic disease was detected in the lungs in 14 patients (30%), in the liver in five patients (11%), in the bone in two patients (4%), in the mediastinal limphonodes in two patients (4%) and in the skin in one patient (2%).

Table I. Patient characteristics.

Gender	
Male	41
Female	6
Age	
Median (range)	60 (41–76)
ECOG PS	
0, 1	**43**
2	4
Histology	
SCC	46
Undiff ca	1
Site of primary	
Oral cavity	12
Oropharynx	13
Hypopharynx	2
Larynx	18
Nasal cavity and paranasal sinuses	2
Disease status	
Locoregional	28
Metastatic	5
Locoregional and metastatic	14
Pretreatment	
None	6
Surgery	5
Radiotherapy	6
Surgery and radiotherapy	30
Chemotherapy	0

Overall, 164 courses of chemotherapy were administered with a median number of 4 (range: 0–5). One patient never started the treatment, six patients received only one course of treatment because of refusal of further treatment (two patients), ineligibility (one patient) or early interruption due to acute heart failure (one patient), peritonitis (one patient), and hemorrhage from the tumor (one patient). Nine patients had two courses then stopped because of progression of disease (eight patients) or poor clinical conditions despite the achievement of a partial response (one patient). Two patients received three courses, 11 patients four and 18 patients five.

No patients needed a reduction of drugs dose. Eighty-five percent of chemotherapy courses were administered without delay. Delays, however, were caused due organizational reasons. Ninety percent of the patients received more than 80% of the planned drugs dose intensity.

Toxicity

Fourty-six patients are considered evaluable for toxicity because one patient never started the treatment. No allergic reactions to paclitaxel were recorded. Details on side effects are given in Table II. The most frequent toxicity was haemathological. Grade III–IV neutropenia was recorded after 41/164 courses of chemotherapy (25%) Almost one half of the patients experienced at least one episode of grade III–IV neutropenia at nadir. However, no episode of febrile neutropenia was recorded. The median duration of neutropenia was three days. Twenty-two percent of the patients had a haemoglobin level between 10.0 and 8.0 g/dl during the treatment. In only two patients (4%) the haemoglobin level dropped under 8.0 g/dl. Six patients were transfused with a total of 21 units of blood. Thrombocytopenia was observed in 48% of the patients; it was severe in 6%. Mucositis occurred in 17% of the patients, but it was severe in only one case. Diarrhea occurred in 8% of the patients and it was grade I or II in most of the cases. Grade I neuro-sensory toxicity was experienced by 15% of the patients. It was of grade II in only one case. One patient had severe neuromotorial side effects.

Responses

Fourty-five patients are considered in the response analysis because one patient never started the treatment and one patient was considered not eligible after the first course of chemotherapy because at that time a dissecting abdominal aortic aneurysm was

Table II. Toxicity (46 evaluable patients).

	WHO grade			
	1 (%)	2 (%)	3 (%)	4 (%)
Leukopenia	1 (24)	6 (13)	11 (24)	3 (7)
Neutropenia	6 (13)	5 (11)	13 (28)	9 (20)
Thrombocytopenia	16 (35)	3 (7)	2 (4)	1 (2)
Anemia	33 (72)	10 (22)	2 (4)	–
Diarrhea	2 (4)	1 (2)	1 (2)	–
Mucositis	5 (11)	2 (4)	–	1 (2)
Nausea/Vomiting	10 (22)	1 (2)	2 (4)	–
Arthralgia/Myalgia	4 (9)	1 (2)	1 (2)	–
Neurotox sensory	7 (15)	1 (2)	–	–
Neurotox motor	–	–	1 (2)	–
Alopecia	3 (6)	15 (33)	12 (26)	5 (11)
Fever without infection	1 (2)	1 (2)	–	–

incidentally detected. Six patients (13.3%) stopped the treatment before being evaluated and are considered as early interruptions. Six patients reached a complete response (13.3%) and eight a partial response (17.8%). The overall response rate was 31.1%. Seventeen patients had stabilization of the disease (37.8%) and eight progressed under therapy (17.8%).

An objective response was achieved in 7/27 patients with loco-regional relapse only (25.9%) and in 7/18 patients with distant metastases (39%). The difference is not statistically significant (Table III).

Median overall progression free survival and median overall survival were 4.1 months (95% C.I.: 2.7–4.1) and 7.9 months (95% C.I.: 4.9–11.1). One-year overall progression free survival and overall survival were16% and 29% respectively. Median progression free survival was 8.7 months (95% C.I.: 6.0–13.3) for patients who responded to the treatment and 2.6 months (95% C.I.: 1.7–3.9) for those who did not. The difference was statistically significant ($p = 0.0025$).

Median survival was 15.9 months (95% C.I.: 11.1–22.3) for patients who responded to the treatment and 5.0 months (95% C.I.: 3.9–7.8) for those who did not. Also this difference was statistically significant ($p = 0.0048$). Median survival is 9.4 months (95% C.I.: 5.8–11.1) for patients with locoregional disease only and 4.9 months (95% C.I.: 3.3–18.7) for those with metastatic disease also. The difference, however, was not statistically significant.

Discussion

The role of taxanes in squamous cell carcinoma of the head and neck is still debated. Despite the promising results from preliminary phase II trials, the combination of paclitaxel and cisplatin showed the same activity and efficacy of the standard cisplatin and 5-fluorouracil regimen in a large randomized trial performed on patients with relapsed disease [13]. The substitution of 5-fluorouracil with paclitaxel, however, seems to reduce toxicity, particularly in terms of acute mucositis. An open question is now if adding paclitaxel to cisplatin and 5-fluorouracil may enhance the activity of the standard doublet.

In our multicenter study this three-drug combination was administered to patients with local recurrence and/or distant metastases who were never treated before with chemotherapy, neither in a chemoradiation front-line program. This combination, at the doses and schedule employed, showed a very safe toxicity profile. Even if one-half of the patients had at least one episode of grade III–IV neutropenia during the treatment, it was of short duration in any case and was never complicated by fever. Moreover only one patient suffered for severe acute mucositis while with the standard cisplatin/5-fluorouracil regimen in which 5-fluorouracil is administered by continous infusion the incidence of grade III–IV mucosal toxicity usually reported is between 15 and 20%. The activity showed (31.1% Objective Response, 13.3% Complete Response) however, is in the range of that reported in randomized trials with the standard cisplatin/5-fluorouracil regimen [6–8] and very similar to that observed with our cisplatin/5-fluorouracil bolus regimen [9]. Even the median progression free survival (4.1 months) and overall survival (7.9 months) are in the range of that reported in the literature during the last two decades. In our experience patients with metastatic disease seem to have a greater chance of response to the treatment than those with locoregional disease only (39% vs 26%) even if the difference does not reach the statistical significance. It is likely that the changes of vascular perfusion in the

Table III. Overall Response Rates (ORR) and median survival (mSURV) according to disease status.

	Overall (45 pts)	Locoregional relapse only (27 pts)	Metastatic disease (18 pts)
ORR	31.1%	25.9%	p = n.s. 39%
mSURV	7.9 months (95% C.I.: 4.9–11.1)	9.4 months (95% C.I.: 5.8–11.1)	p = n.s. 4.9 months (95% C.I.: 3.3–18.7)

Table IV. Trials on combinations of Cisplatin, 5Fluorouracil and Paclitaxel.

	DISEASE STATUS	PHASE	N	DRUGS	CR%	ORR%	mSURV
Benasso	recurrent	II	47	P, DDP, 5FU bolus	13	31	7.9
Hussain [18]	recurrent	II	19	P, DDP, 5FU c.i.	21	58	6
Worden[19]	recurrent	II	65	P, DDP, 5FU c.i	5	37	9
Hitt [20]	recurrent	II	24	P, DDP, 5FU c.i., LLV	46	83	17
Hitt [21]	local. adv.	II	70	P, DDP, 5FU c.i	59	88	n.s.
Hitt [22]	local. adv.	III	192	P, DDP, 5FU c.i.	33*	86	n.s.
			192	DDP, 5FU c.i.	14*	75	n.s.

P: paclitaxel, DDP: cisplatin, 5FU: 5-flurouracil; CR: complete response; ORR: overall response rate; n.s.: not stated; *: $p = 0.000$.

tissues nearby the local relapse due to pretreatments (radiation and/or surgery) may play a role in this outcome. Despite this observation, however, patients with distant metastases still seem to have a worse prognosis.

In conclusion, even considering the limits of a phase II trial, results from our study seem not to suggest a superiority of the triplet including paclitaxel, cisplatin and 5-fluorouracil over the combinations of cisplatin and 5-fluorouracil or cisplatin and paclitaxel in patients with relapsed disease pretreated with surgery and/or radiation.

The three drug combination has been investigated on patients with relapsed disease in other three phase II trials (Table IV). Results of only two are reported in full papers. In the first trial [18], cisplatin, paclitaxel and 5-FU by continous infusion gave a response rate higher (58%) than that observed in our trial, but the sample size was very small (only 19 patients) and median survival was on the lower limit of the range reported in the literature (6 months).

In the second trial [19] this triplet resulted in a 37% overall response rate and a median survival of 9 months on 65 evaluable patients. In this case a high toxicity, particularly on the mucosas, was observed.

In the third trial the same triplet with the addition of leucovorin in a "dose-dense" schedule was explored [20]. In this case a surprising 83% overall response with a median survival of 17 months was observed on 24 patients with relapsed disease. These results are unique in the head and neck literature and may be justified only by a high selection of the study population, as stated by the authors in the paper.

Things seem to be different in patients with previously untreated disease. Recently, in a large randomized trial [21] the combination of paclitaxel, cisplatin and 5-fluorouracil gave higher complete response rate and better progression free survival in comparison with cisplatin and 5-fluorouracil administered as induction chemotherapy to patients with advanced, previously untreated, squamous cell carcinoma of the head and neck before a definitive concomitant chemoradiation (Table IV). Results from this study re-evaluate the role of induction chemotherapy and, in the meantime, supports the inclusion of paclitaxel into the standard doublet in this subset of patients.

Docetaxel containing regimens have been less investigated at now. In relapsed disease phase II studies of docetaxel in combination with cisplatin gave response rates similar to those achievable with cisplatin and 5-fluorouracil [23,24] but data of comparison of the two regimens from a randomized trial are not yet available. Moreover, data on the triplet including cisplatin, docetaxel and 5-fluorouracil are lacking.

Also in this case, however, results seem more promising in previously untreated patients (Table V). Very recently, a large phase III trial from the EORTC [28] demonstrated that adding docetaxel to cisplatin and 5-fluorouracil significantly increases response rate, progression free survival and overall survival in patients with locally advanced disease subsequently treated with definitive radiation.

In conclusion, it appears that in patients with squamous cell carcinoma of the head and neck

Table V. Trials on combinations of Cisplatin, 5Fluorouracil and Docetaxel.

	DISEASE STATUS	PHASE	N	DRUGS	CR%	ORR%
Posner [25]	local. adv.	II	43	D, DDP, 5FU c.i.	40	93
Colevas [26]	local. adv.	II	34	D, DDP, 5FU c.i., LLV	44	94
Schrijvers [27]	local. adv.	II	48	D, DDP, 5FU c.i.	0	64–78
Vermorken [28]	local. adv.	III	177	D, DDP, 5FU c.i.	n.s.	68*
			181	DDP, 5FU c.i.	n.s.	54*

DDP: cisplatin, 5FU: 5-flurouracile, D: docetaxel; CR: complete response; ORR: overall response rate; *: $p = 0.016$.

relapsed after surgery and/or radiation the combination of cisplatin and paclitaxel is at least equivalent to cisplatin and 5-fluorouracil in terms of activity and efficacy but it is less toxic on the mucosas. Data from phase II trials, including ours, seem not to support the administration of the three drugs together in a palliative setting.

Conversely, in patients with previously untreated disease, the inclusion of a taxane (paclitaxel or docetaxel) into a cisplatin/5-fluorouracil induction regimen may improve prognosis. Confirmatory trials are warranted in this field.

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References

[1] Kish SG, Weaver A, Jacobs, Cummings G, Al-Sarraf M. Cisplatin and 5-fluorouracil infusion in recurrent and disseminated epidermoid cancer of the head and neck. Cancer 1984;53:1819–24.

[2] Rowland KM, Taylor SG, Spiers AS, DeConti RC, O'Donnell MR, Showel J, et al. Cisplatin and 5-fluorouracil infusion chemotherapy in advanced recurrent cancer of the head and neck. An Eastern Cooperative Oncology Group pilot study. Cancer Treat Rep 1986;70:461–4.

[3] Creagan ET, Ingle JN, Shutt AJ, O'Fallon JR. A phase II study of cis-diamminedichloroplatinum and 5-fluorouracil in advanced upper aerodigestive neoplasm. Head Neck Surg 1984;6:1020–3.

[4] Dasmahaparta KS, Citrin P, Hill GJ, Yee R, Mohit-Tabatabai MA, Rush BF Jr. A prospective evaluation of 5-fluorouracil plus cisplatin in advanced squamous cell cancer of the head and neck. J Clin Oncol 1985;3:1486–9.

[5] Amrein PC, Weitzam SA. Treatment of squamous cell carcinoma of the head and neck with cisplatin and 5-fluorouracil. J Clin Oncol 1985;3:1632–9.

[6] Jacobs C, Lyman G, Velez-Garcia E, Sridhar KS, Knight W, Hochster H, et al. A phase II randomized study compariting cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. J Clin Oncol 1992;10:257–63.

[7] Forastiere A, Metch B, Schuller D, Ensley JF, Hutchins LF, Triozzi P, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous cell carcinoma of the head and neck. A Southwest Oncology Group study. J Clin Oncol 1992;10:1245–51.

[8] Clavel M, Vermorken JB, Cognetti F, Cappelaere P, de Mulder PH, Schornagel JH, et al. Randomized comparison of cisplatin, methotrexate, bleomycin and vincristin (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastic squamous cell carcinoma of the head and neck. A phase III study of the EORTC Head and Neck Cancer Cooperative Group. Ann Oncol 1994;5:521–6.

[9] Merlano M, Tatarek R, Grimaldi A, Margarino G, Rossa R. Phase I-II trial with cisplatin and 5-FU in recurrent head and neck cancer: An effective outpatient schedule. Cancer Treat Rep 1985;69:961–4.

[10] Merlano M, Vitale V, Rosso R, Benasso M, Corvo R, Cavallari M, et al. Treatment of advanced squamous cell carcinoma of the head and neck with alternating chemotherapy and radiotherapy. N Engl J Med 1992;327:1115–21.

[11] Forastiere A, Shank D, Neuberg D, Taylor SG, DeConti RC, Adams G, et al. Final report of a phase II evaluation of paclitaxel in patients with advanced squamous cell carcinoma of the head and neck: an Eastern Cooperative Oncology Group trial (PA390). Cancer 1998;82:2270–4.

[12] Forastiere AA, Leong T, Rowinsky E, Murphy BA, Vlock DR, DeConti RC, et al. Phase III comparison of high-dose paclitaxel+cisplatin+granulocyte colony-stimulating factor versus low-dose paclitaxel+cisplatin in advanced head and neck cancer: Eastern Cooperative Oncology Group Study E1393. J Clin Oncol 2001;19:1088–95.

[13] Murphy B, Li Y, Cella D, Karnad M, Hussain A, Forestiere A, et al. Phase III Study Comparing Cisplatin (C) & 5-Fluorouracil (F) Versus Cisplatin & Paclitaxel (T) in Metastatic/Recurrent Head & Neck Cancer (MHNC). Proc ASCO 2001;20:224 (abstr 894).

[14] Benasso M, Numico G, Rosso R, Merlano M, Ricci I, Gentile A. Chemotherapy for relapsed head and neck cancer: paclitaxel, cisplatin, and 5-fluorouracil in chemotherapy-naive patients. A dose-finding study. Semin Oncol 1997;24(6 Suppl 19):S19-46–50.

[15] Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47:207–10.

[16] Thall PF, Simon R, Ellenberg SS. A two-stage design for choosing among several experimental treatments and a control in clinical trials. Biometrics 1989;45:537–47.

[17] Kaplan EL, Meyer P. Non-parametric estimation for incomplete observation. J Am Stat Assoc 1958;53:457–74.

[18] Hussain M, Gadgeel S, Kucuk O, Du W, Salwen W, Ensley J. Paclitaxel, cisplatin, and 5-fluorouracil for patients with advanced or recurrent squamous cell carcinoma of the head and neck. Cancer 1999;86:2364–9.

[19] Worden FP, Moon J, Samlowski W, Clark J, Dakhil SR, Taylor SA, et al. A phase II evaluation of a 3-hour infusion of paclitaxel (P), cisplatin (CDDP) & 5-fluorouracil (5FU) in patients with advanced or recurrent squamous cell carcinoma of the head & neck (SCCHN): A Southwest Oncology Group Study. Proc ASCO 2004;22:491 (abstr 5512).

[20] Hitt R, Jimeno A, Millan JM, Castellano D, Cortes-Funes H. Phase II trial of dose-dense paclitaxel, cisplatin, 5-fluorouracil, and leucovorin with filgrastim support in patients with squamous cell carcinoma of the head and neck. Cancer 2004;101:768–75.

[21] Hitt R, Paz-Ares L, Brandáriz A, Castellano D, Pena C, Millan JM, et al. Induction chemotherapy with paclitaxel, cisplatin and 5-fluorouracil for squamous cell carcinoma of the head and neck: long-term results of a phase II trial. Ann Onc 2002;13:1665–73.

[22] Hitt R, Lopez-Pousa A, Rodriguez M, Martinez-Trufero J, Cervantes A, Carles J, et al. Phase III study comparing cisplatin (P) & 5-fluorouracil (F) versus P, F and paclitaxel (T) as induction therapy in locally advanced head & neck cancer (LAHNC). Proc ASCO 2003;22:496 (abstr 1997).

[23] 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.

[24] Gedlicka C, Formanek M, Selzer E, Burian M, Kornfehl J, Fiebiger W, et al. Phase II study with docetaxel and cisplatin in the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck. Oncology 2002;63:145–50.

[25] Posner MR, Glisson B, Frenette G, Al-Sarraf M, Colevas AD, Norris CM, et al. Multicentre phase I–II trial of docetaxel, cisplatin, and fluorouracil induction chemotherapy for patients with locally advanced squamuos cell cancer of head and neck. J Clin Oncol 2001;19:1096–104.

[26] Colevas AD, Norris CM, Tishler RB, Lamb CC, Fried MP, Goguen LA, et al. Phase I/II trial of outpatient docetaxel, cisplatin, 5-fluorouracil, leucovorin (opTPFL) as induction for squamous cell carcinoma oof the head and neck (SCCHN). Am J Clin Oncol 2002;25:153–9.

[27] Schijvers D, Van Herpen C, Kerger J, Joosens E, Van Laer 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.

[28] Vermorken JB, Remenar E, Van Herpen C, Germa Lluch J, Stewart S, Gorlia T, et al. Standard cisplatin/infusional 5-fluorouracil (PF) vs docetaxel (T) plus PF (TPF) as neoadjuvant chemotherapy for nonresectablelocally advanced squamous cell carcinoma of the head and neck (LA-SCCHN): a phase III trial of the EORTC Head and Neck Cancer Group. Proc ASCO 2004;22:490 (abstr 5508).