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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

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Abstract

A combination of cisplatin and 5-fluorouracil (PF) is considered the standard induction chemotherapy regimen for squamous cell carcinoma of the head and neck (SCCHN). The present study compares the efficacy and safety of a new combination of cisplatin/docetaxel *versus* the PF regimen. A total of 83 chemotherapy-naïve patients with locally advanced SCCHN were randomised to receive every 21 d (i) docetaxel 85 mg/m^2 i.v. on day 1 and cisplatin 40 mg/m^2 i.v. on days 1 and 2 (arm A) or (ii) cisplatin 100 mg/m^2 i.v. on day 1 followed by 5-fluorouracil 1000 mg/m^2 in 24 h continuous infusion for 5 d (arm B). A total of 287 cycles (range 1–3 per patient) were administered. Among 76 patients evaluable for response, the overall response rate in arm A was 70% (complete response (CR) 26%, partial response (PR) 44%) and in arm B 69% (CR 16%, PR 54%), respectively. Median survival in arm A was 7.6 months (95% CI: 5.8–11.1) and 9.9 months (95% CI: 7.4–14.6) for arm B. The most frequent grade 3/4 toxicity in arm A was neutropaenia (34.1%) and diarrhoea (9.8%) *versus* mucositis (29.3%) and neutropaenia (19.5%) in arm B. Both schedules present a similar efficacy, with different but acceptable toxicity patterns.

Keywords: Docetaxel; Cisplatin; 5-Fluororacil; 5-FU; Neoadjuvant; SCCHN; Head and neck

1. Introduction

Squamous cell carcinoma of the head and neck (SCCHN) represents 5% of new diagnoses of cancer, with more than 400,000 new cases annually worldwide. Although it is potentially curable with surgery or radiotherapy in the early stages, relapses are present in 10–40% of cases, and locally advanced SCCHN (stage III–IV) is frequently present among patients at their first visit [1]. Chemotherapy and/or radiotherapy has been considered the standard therapy for non-resectable tumours. For operable disease, surgery followed by

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radiotherapy was the most accepted treatment. However, the cure rate does not exceed 30%, with a high rate of locoregional failure (60%) or distant metastasis (20%) [2]. Induction chemotherapy, based on cisplatin, has been used since the 1970s, and although its use is controversial because it has not showed a consistent significant benefit in terms of survival, organ preservation and reduction in the rate of distant metastases have been made possible with this approach [3–7]. 5-Fluorouracil (5-FU) is an anti-metabolite drug with anti-tumour activity in head and neck cancer. When given as a prolonged continuous infusion, stomatitis and diarrhoea are the principal dose-limiting toxicities (DLTs) [8]. Because 5-FU has a demonstrated synergistic interaction with many anti-neoplastic agents, currently it is most often administered in the setting of combination chemotherapy regimens. The induction chemotherapy of cisplatin plus 5-FU (PF regimen) has been the standard combination in the treatment of locally advanced and recurrent SCCHN [6,9]. In randomised trials, response rates to PF ranged from 60% to 80% and clinical complete response (CR) rates were in a range of 20–30% [10].

Docetaxel is a taxoid cytotoxic agent with considerable clinical activity in a broad range of malignancies. Its mechanism of action is through stabilisation of tubulin, arresting cells in the G2M phase of the cell cycle. Single-agent docetaxel (D) administered at the maximum tolerated dose of 100 mg/m^2 as a 1-h infusion every 3–4 weeks initiated an overall response of 20–45% with a duration of 5–6.5 months in patients with recurrent locoregional or metastatic SCCHN [11–13]. Overall, docetaxel-based induction regimen in chemotherapy-naïve patients gave a universal CR for primary disease and a 57% CR for nodal involvement, as well as a well-balanced safety profile with gastrointestinal infection and short-lasting, non-cumulative neutropaenia rarely complicated by fever [14]. Additionally it is known that fractionated administration of cisplatin (P) apparently increases the therapeutic index of the combination in the induction therapy in patients with advanced NSCLC [15].

In the present phase II study, the Spanish Group of Treatment of Head and Neck Tumours (TTCC) evaluated two chemotherapy combinations, docetaxel plus fractionated cisplatin (DP) *versus* standard cisplatin plus 5-FU (PF), in chemotherapy-naïve patients with locally advanced SCCHN, in order to determine the best induction chemotherapy for phase III studies, according to the tumour responses and safety profiles.

2. Patients and methods

2.1. Patients

Eligibility criteria for admission to the study were as follows: (i) histologically confirmed, locally advanced SCCHN of oral cavity, oropharynx, larynx or hypopharynx in stage III–IV without evidence of distant metastases; (ii) no prior chemotherapy or radiation therapy; (iii) having at least one measurable lesion in one dimension; (iv) age <75 years with Eastern Cooperative Oncology Group (ECOG) $\leqslant 2$; (v) adequate haematological function with neutrophil count $\geqslant 1500$/ml, platelets $\geqslant 100{,}000$/ml and haemoglobin $\geqslant 10$ g/ml; (vi) adequate hepatic function with bilirubin $\leqslant 1\times$ the upper normal limit, GOT and GPT $\leqslant 2.5\times$ the upper normal limit and alkaline phosphatase $\leqslant 5\times$ the upper normal limit; (vii) renal function within normality with serum creatinine $\leqslant 1.4$ mg/dl and creatinine clearance $\geqslant 60$ ml/min calculated by the Cockcroft–Gault method.

Patients who did not fulfil the established inclusion criteria as well as those who had peripheral neuropathy or other serious diseases (unstable ischaemic heart disease, acute myocardial infarction 6 months prior to inclusion, history of significant neurological or psychiatric disorder or active peptic ulcer) or who were being treated concomitantly with corticosteroids (except as pre-medication) were excluded from the study. Additionally, patients who had another type of neoplasm were excluded.

The study was developed according to GCP guidelines and approved by local ethics committee at each participating institution. Written informed consent was obtained from each patient by the investigator.

2.2. Treatment schedule

The patients were stratified according to tumour site (oral cavity, oropharynx, hypopharynx and larynx) and were centrally randomised to receive one of the two treatment regimens. The arm A chemotherapy regimen consisted of docetaxel 85 mg/m^2 as a 1-h infusion on day 1 and cisplatin at a dose of 40 mg/m^2 as a 30-min infusion after hyperhydration on days 1 and 2. The arm B regimen consisted of cisplatin at a dose of 100 mg/m^2 as a 1–3-h infusion on day 1, followed by 5-FU 1000 mg/m^2 as a continuous 24-h infusion over 5 d in every cycle. Both schedules were repeated every 21 d, and 4 cycles were planned. After induction chemotherapy patients received locoregional treatment according to the standard clinical practice at each participating centre.

In arm A, pre-medication included prophylactic treatment with oral dexamethasone 8 mg for a total of six doses. During treatment standard anti-emetic treatment with ondansetron was administered. Therapeutic and prophylactic administration of granulocyte-colony stimulating factor (G-CSF) was allowed in case of treatment-induced neutropaenia.

2.3. Dose modification

Regarding haematological toxicity, subsequent cycles were delayed for 1 week (usual recovery time) if grade 1

and 2 toxicities appeared. The dose of docetaxel was reduced by 20% in the following cycle if grade 4 myelosuppression was present. In case of a second episode of myelosuppression (neutropaenia) an additional 20% reduction of the docetaxel dose was applied, while if there was a third episode the drug was discontinued. Cisplatin and 5-FU doses were not changed.

In case of non-haematological toxicity, treatment was delayed until recovery, but for not more than 2 weeks. Treatment was discontinued in the case of stomatitis or diarrhoea of grade 4. The 5-FU dose was reduced by 20% if there was stomatitis and diarrhoea of grade 3 and discontinued when an aggravation to grade 4 was observed. Cisplatin was reduced by 20% if grade 2 neuropathy appeared. In case of cisplatin-induced grade 3 neuropathy, the patient was subsequently withdrawn from the study. If 24-h creatinine clearance decreased between 40 and 59 ml/min, cisplatin was reduced by 50% and discontinued if the clearance was lower than 40 ml/min.

2.4. Assessments of response and toxicity

Response assessment was performed after the administration of the second cycle and at the end of study with the same procedures used in the diagnosis and following the World Health Organisation (WHO) response criteria [16]. The clinical response was assessed for each patient according to combined findings of physical examination, cervical-thoracic computed tomography (CT), magnetic resonance imaging (MRI) and panendoscopy with biopsy sampling of the primary site. Eligibility to assess efficacy was considered when at least two cycles of chemotherapy had been received, while all patients were evaluable for toxicity. Toxicity was graded according to Common Toxicity Criteria (CTC) of the National Cancer Institute (NCI) V.1.0 [17].

2.5. Statistical analysis

A randomised phase II design was used to determine the overall response rate of both induction chemotherapy regimens, and the feasibility and tolerance. Patients were assigned randomly to arms to obtain unbiased estimates of the differences between the average effects of PF and DP on patient outcome.

The clinical CR rate was the main end-point. Within each treatment arm, the Simon design was based on a test of a null hypothesis of 0.40 *versus* an alternative of 0.55. With type II error rate at 10%, 42 patients by group were required.

Absolute frequencies and percentages were used to describe the categorical variables. All failure-time endpoints were calculated from the date of randomisation. Survival and time to progression rates were calculated using the Kaplan–Meier method. For continuous variables, the sample size, mean, standard deviation (SD), median and range were obtained The standard package of SAS® system was used to make the database as well as to carry out the statistical analysis.

3. Results

3.1. Characteristics of patients

Between February 2000 and July 2001, 84 patients with locally advanced resectable and non-resectable SCCHN were included in the study. Baseline patient characteristics are summarised in Table 1. All patients had stage III or IV disease (85.5% stage IV). The overall median age was 56.5 years (range 38–71 years) and 94% ($n = 78$) were men. The most frequent primary site of cancer was the larynx (31.3%), followed by the oropharynx (28%), hypopharynx (24%) and oral cavity (17%). A total of 31% of patients from arm A and 22% from B were T4N2.

3.2. Treatment

For the response evaluation, 76 patients who had received at least 2 cycles of treatment were assessed (39 in arm A and 37 in arm B; Fig. 1). A total of 287 cycles were administered (144 in arm A and 143 in arm B), with a mean of 3 cycles (range 1–3) per patient in both groups. Treatment was delayed due to toxicity in 36 cycles in arm A and in 60 in arm B. The docetaxel dose

Table 1
Patient characteristics ($n = 83$)

Characteristics	Arm A $n = 42$; n (%)	Arm B $n = 41$; n (%)
Age (years)	58	55
Gender		
Male	40 (48)	38 (46)
Female	2 (2)	3 (4)
ECOG		
0	14 (33)	14 (37)
1	28 (67)	26 (63)
Primary site		
Larynx	12 (29)	14 (34)
Oropharynx	10 (24)	13 (32)
Hypopharynx	11 (26)	9 (22)
Oral cavity	9 (21)	5 (12)
Histological grade		
G 1	12 (29)	4 (10)
G 2	10 (24)	12 (29)
G 3	8 (19)	12 (29)
G 4	2 (5)	1 (3)
Unknown	10 (24)	12 (29)
Stage		
III	6 (14)	6 (15)
IV	36 (86)	35 (85)

ECOG, Eastern Cooperative Oncology Group.

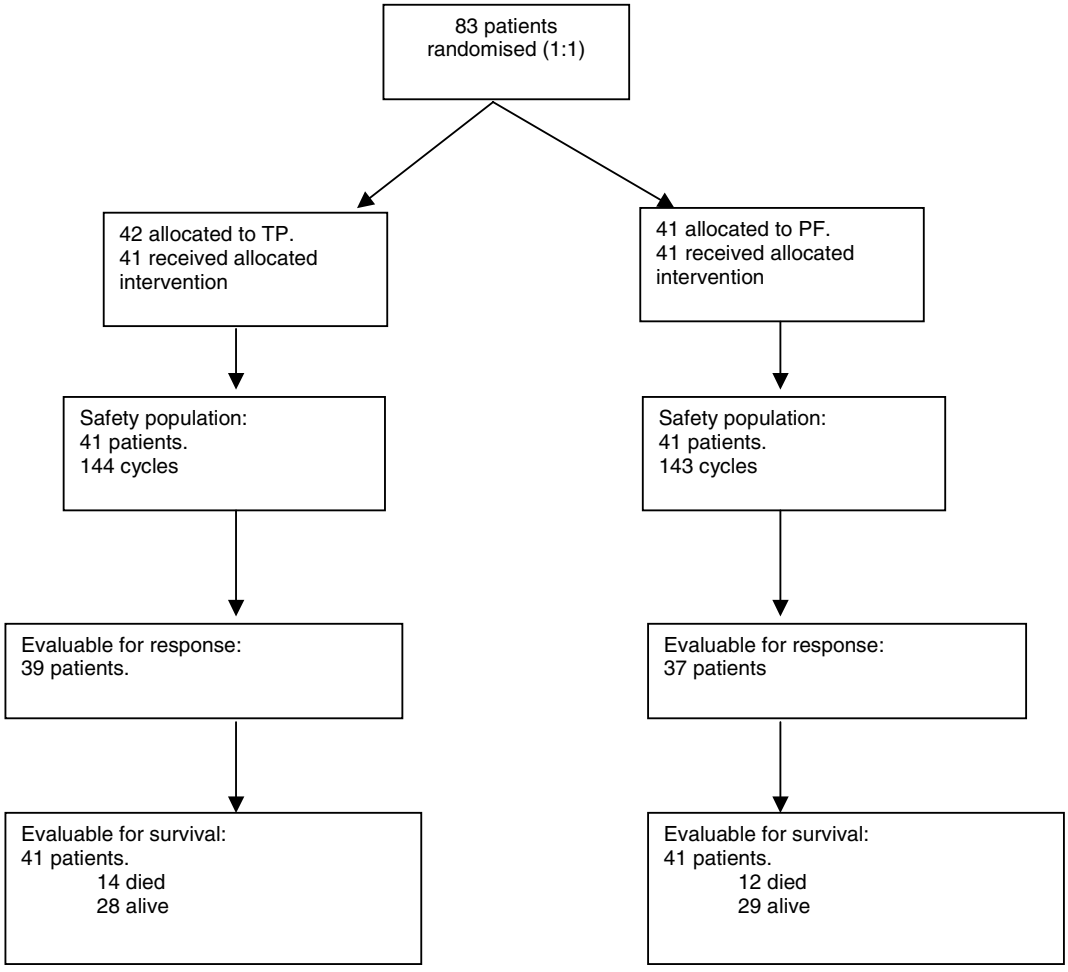

Fig. 1. Progress of patients through the trial. PF, combination of cisplatin and 5-fluorouracil; TP, docetaxel/cisplatin.

was decreased in only 2 cycles, while 5-FU and cisplatin were decreased in 8 and 5 cycles, respectively. Relative dose intensity in arm A was 0.92 for docetaxel and 0.91 for cisplatin, while in arm B it was 0.87 for cisplatin and 0.76 for 5-FU.

Response rate obtained in the trial is summarised in Table 2. The overall clinical response to treatment in arm A was present in 27 of the 39 evaluable patients (70%) with 26% CRs and, in arm B, in 26 of the 37 evaluable patients (70%) with 16% CRs.

Survival was not a statistical end-point for this study. However, survival information was retrieved for all patients. Overall, 27 patients developed disease progression (15 in arm A and 12 in arm B), and 26 patients died (14 and 12, respectively). Median survival for arm A was 7.6 months (95% CI: 5.8–11.1) and 9.9 months (95% CI: 7.4–14.6) for arm B, the 12-month survival rate was 30% in both groups (Fig. 2).

Table 2
Response to chemotherapy treatment ($n = 76$)

	Docetaxel/cisplatin arm A ($n = 39$)		Cisplatin/5-FU arm B ($n = 37$)	
	n	% (95% CI)	*n*	% (95% CI)
Complete response	10	26 (13–42)	6	16 (6–32)
Partial response	17	44 (28–60)	20	54 (37–71)
Overall response rate	27	69.2 (NA)	26	70.2 (NA)
Stable disease	9	23 (11–39)	7	19 (8–35)
Progressive disease	3	7 (1–21)	4	11 (3–25)
Median survival (months)	7.6	5.8–11.1	9.9	7.4–14.6
One-year survival (%)	30	NA	30	NA

NA, not available; 5-FU, 5-fluorouracil; CI, confidence interval.

3.3. Toxicity

Overall, 82 of the 83 patients were included in the safety analysis; one patient was considered non-eligible due to incorrect inclusion and he never received treatment. Two toxic deaths were recorded, one in each arm. The most frequent grade 3/4 toxicity in arm A was neutropaenia (34.1% of patients) and overall 17.1% of patients developed febrile neutropaenia, diarrhoea (9.8%), and asthenia (9.8%). In those patients receiving the PF regimen, the most frequent grade 3 or 4 toxicity was mucositis (29.3%),

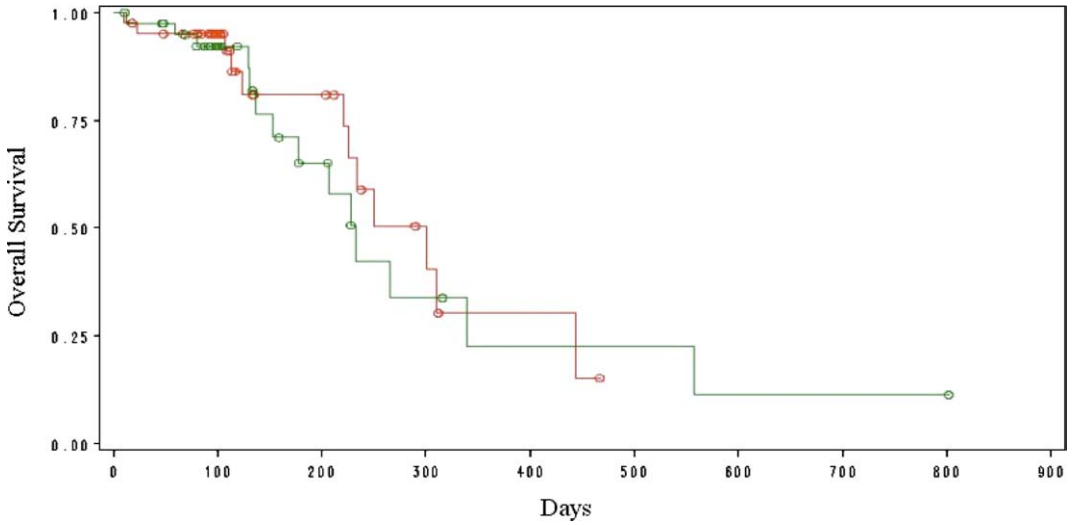

Fig. 2. Overall survival by treatment arm ($n = 82$).

Table 3
Grade 3–4 NCI CTC treatment-related toxicity ($n = 82$)

Toxicity	Docetaxel/cisplatin $n = 41$; n (%)	Cisplatin/5-FU $n = 41$; n (%)
Haematological		
Anaemia	1 (2.4)	–
Neutropaenia	14 (34.1)	8 (19.5)
Neutropaenic fever	7 (17.1)	2 (4.9)
Non-haematological		
Nausea	–	3 (7.3)
Vomiting	–	5 (12.2)
Stomatitis	3 (7.3)	12 (29.3)
Diarrhoea	4 (9.8)	2 (4.9)
Skin	1 (2.4)	–
Infection	2 (4.9)	2 (4.9)
Asthenia	4 (9.8)	–
Weight loss	1 (2.4)	1 (2.4)

CTC, Common Toxicity Criteria; NCI, National Cancer Institute; 5-FU, 5-fluorouracil.

neutropaenia (19.5%) and nausea and vomiting (19.5%) (Table 3).

4. Discussion

Considerable progress has been made in the treatment of patients with locally advanced head and neck cancer in the last years. This improvement has resulted in a better local control, higher quality of life and organ preservation in a considerable number of patients, as well as disease-free and overall survival [5,7,9].

Numerous studies have explored the induction chemotherapy cisplatin/5-FU combination (with or without concurrent or sequential radiotherapy) in the treatment of SCCHN. Neoadjuvant chemotherapy have shown to be effective in preserving organ function by reducing the need for mutilating surgery in patients with resectable tumours of the larynx and hypopharynx [6,7] and/or improving survival in patients with unresectable disease [18–21]. The induction chemotherapy of cisplatin plus 5-FU (PF regimen) has been the standard combination in the treatment of locally advanced and recurrent SCCHN [6,9]. However, neoadjuvant chemotherapy has not showed a significant impact on survival in most trials, although a meta-analysis found a small but significant impact on survival when only the cisplatin-containing regimens are considered [5]. Although single trials have not shown a significant benefit of induction chemotherapy in terms of survival, a recent meta-analysis has shown that full-dose PF significantly improves survival in patients with locally advanced SCCHN, resulting in a significant 16% reduction in the risk of death in curatively treated patients compared with controls [5,11,12]. Additionally, in patients with non-resectable disease, recently updated results confirm that the use of induction chemotherapy improves survival when compared with radiotherapy alone [13]. More consistent are the results with concurrent chemo-radiation, reinforced by a recent updated meta-analysis, in which the improvement in overall survival, mainly when cisplatin is included, is clear when compared with radiotherapy alone [6]. Moreover, it is well established that, PF-based induction chemoradiotherapy is effective in replacing surgery for organ preservation in tumours of the larynx and hypopharynx [6].

Monotherapy with docetaxel has shown to be effective in SCCHN in multiple phase II studies, with a different mechanism of action and toxicity profile compared with the PF regimen [13,22,23]. Docetaxel's major dose-limiting toxicity (DLT) was a dose- but not schedule-dependent neutropaenia followed by schedule-dependent grade 3 mucositis, whereas myelotoxicity of cisplatin/5-FU regimen is usually mild. Results

using combinations of docetaxel with other chemotherapy agents with different schedules and different synergy have already been published. However, results with a new combination chemotherapy of docetaxel/5-FU (TF) in incurable SCCHN patients showed that the response rate to TF regimen (24%) was lower than expected [24]. Docetaxel-based doublet or triplet combinations in both recurrent and neoadjuvant SCCHN have demonstrated additional improvement in toxicity and overall survival results. When used in combination with 5-FU, docetaxel (TF regimen) induced response rates of 24% with median survival of 9.6–11 months [24]. One study has reported that combination cisplatin/docetaxel achieves overall responses of 52.5% in previously treated patients and of 100% in a subgroup of chemotherapy-naïve patients with recurrent and/or metastatic SCCHN [25]. Results from another phase II study of docetaxel/cisplatin (TP) in patients with SCCHN reported a slightly better overall response rate of 33% (8 of 24 patients) with CR in 8% and PR in 25% of patients [26]. On the other hand, the induction treatment in chemotherapy-naïve patients with combinations of docetaxel and PF regimen (TPF) for advanced SCCHN has shown an overall response as high as 93% with a high rate of primary site clinical and pathological CRs (40%) [27]. The most common toxicities in that study were neutropaenia, mucositis, anaemia, fatigue, alopecia, pain, diarrhoea and nausea.

Colevas and colleagues have reported very high response rates in a phase I/II trial of docetaxel, cisplatin, 5-FU and leucovorin (TPFL5 regimen) induction chemotherapy in patients with locally advanced SCCHN [28]. They observed that the overall response rate to TPFL5 was 100%, with 61% clinical CRs and 39% clinical partial responses (PRs), but with a high-rate of toxicity in the form of neutropaenia, as dose-limiting toxicity, nausea, mucositis, diarrhoea, peripheral neuropathy and sodium-wasting nephropathy.

Analysis of combined docetaxel/PF regimens (TPF regimen) in locally advanced disease resulted in high 2–3-year survival rates and overall response rates across the phase II trials in the range of 42–82% and 71–100%, respectively [18–21]. Moreover, addition of docetaxel to the cisplatin, 5-FU and leucovorin (TPFL-5 regimen) schedule has yielded an overall response rate of 100% and CR rate of 61%, but at the expense of considerable toxicity [23].

Consequently, in the present study we simultaneously compared for the first time the standard induction chemotherapy regimen of cisplatin/5-FU (PF) with a new schedule of cisplatin/docetaxel (TP) in order to optimise chemotherapy of SCCHN patients. Recently the preliminary results of a phase III trial which tests the impact of adding docetaxel to standard neoadjuvant PF have been reported [29].

The overall response rate reached in both groups was 70%, with a similar number of CRs and PRs obtained after a similar number of treatment cycles (144 *versus* 143 in arm A and B). Although a greater percentage of CRs was seen in the docetaxel schedule (arm A 26% *versus* arm B 16%) it did not reach a statistically significant difference. Those results are similar to those reported recently in other TPF regimens [14,18,23,30].

The recent previously mentioned phase III trial was well designed and had a high number of patients, however, the docetaxel/cisplatin/fluorouracil arm has showed a clear advantage in response rate and overall survival when compared with PF. This trial only considered for inclusion patients with non-resectable disease [29].

Treatment-related toxicity is a major concern and disadvantage in combined-modality approaches. We reported that febrile neutropaenia (17.1%) was the most common adverse event observed, with grade 3–4 in the docetaxel/cisplatin group, prevalently due to docetaxel, followed by diarrhoea and stomatitis. Studies with a similar design have reported a higher incidence of neutropaenia. In one study, the most frequent moderate-to-severe toxicity in 75% of patients was grade 3–4 transient neutropaenia with similar rates of other induced adverse events of grade 3–4 [26]. In the cisplatin/5-FU group the most frequent adverse event was stomatitis, which was observed in 29.3% of patients.

In conclusion, in our phase II trial, both schedules, cisplatin/docetaxel and cisplatin/5-FU, are active and useful combinations in patients with locally advanced SCCHN. The high response rates, and recent results of a phase III trial with better survival for docetaxel combination, justify further evaluation of those chemotherapy combinations in major patient populations. Both schedules are well tolerated, with significant but different toxicity patterns, which are generally well manageable.

Conflict of interest statement

None declared.

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References

1. Schantz SP, Harrison LB, Forastiere AA. Tumors of the nasal cavity and paranasal sinuses, nosopharynx, oral cavity and oropharinx. In De Vita Jr VT, Hellman S, Rosenbergg SA, eds. *Cancer: Principles and practice of oncology*. 5th ed. Philadelphia, PA, Lippincorr-Raven, 1977. pp. 741–801.
2. Vokes EE, Weichselbaum RR, Lippman SM, *et al*. Head and neck cancer. *N Engl J Med* 1993, **328**, 184–194.
3. Munro AJ. An overview of randomised controlled trials of adjuvant chemotherapy in head and neck cancer. *Brit J Cancer* 1995, **71**, 83–91.
4. El-Sayed S, Nelson N. Adjuvant and adjunctive chemotherapy in the management of squamous cell carcinoma of the head and neck region. A meta-analysis of prospective and randomized trials. *J Clin Oncol* 1996, **14**, 838–847.
5. Pignon JP, Bourhis J, Domenge C, *et al*. 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**, 949–955.
6. The Department of 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**, 1685–90.
7. Lefebvre JL, Chevalier D, Luboinski B, *et al*. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. *J Natl Cancer Inst* 1996, **88**, 890–899.
8. Grem JL. 5-Fluorouracil: forty-plus and still ticking. A review of its preclinical and clinical development. *Invest New Drugs* 2000, **18**, 299–313.
9. Al-Sarraf M. Treatment of locally advanced head and neck cancer: historical and critical review. *Cancer Control* 2002, **9**, 387–399.
10. Haddad R, Tishler RB, Norris CM, *et al*. Docetaxel, cisplatin, 5-fluorouracil (TPF)-based induction chemotherapy for head and neck cancer and the case for sequential, combined-modality treatment. *Oncologist* 2003, **8**, 35–44.
11. Posner MR. Docetaxel in squamous cell cancer of the head and neck. *Anticancer Drugs* 2001, **12**, S21–S24.
12. Colevas AD, Posner MR. Docetaxel in head and neck cancer: a review. *Am J Clin Oncol* 1998, **21**, 482–486.
13. Glisson BS. The role of docetaxel in the management of squamous cell cancer of the head and neck. *Oncology (Huntingt)* 2002, **16**, 83–87.
14. Schoffski P, Weihkopf T, Ganser A. Advanced head and neck cancer and clinical experience of an effective new agent: docetaxel. *Anticancer Res* 1998, **18**, 4751–4756.
15. Betticher DC, Hsu Schmitz SF, Gautier Y. Neoadyuvant chemotherapy with docetaxe and cisplatin in patients with non small-cell-lung cancer, stage IIIA, N2 is highly active with few toxicitiesl. *Proc Am Soc Clin Oncol* 1999, **18**, 473. [abstract 1824].
16. WHO. *WHO handbook for reporting results of cancer treatment*. WHO Offset Publications; 1979, p. 48.
17. National Cancer Institute. *Guidelines for the reporting of adverse drug reactions*. MD, Division of Cancer Treatment, National Cancer Institute; 1999, p. 1–80.
18. Haddad R, Colevas AD, Tishler R, *et al*. Docetaxel, cisplatin, and 5-fluorouracil-based induction chemotherapy in patients with locally advanced squamous cell carcinoma of the head and neck: the Dana Farber Cancer Institute experience. *Cancer* 2003, **97**, 412–418.
19. Katori H, Tsukuda M, Mochimatu I, *et al*. Phase I trial of concurrent chemoradiotherapy with docetaxel, cisplatin and 5-fluorouracil (TPF) in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN). *Brit J Cancer* 2004, **90**, 348–352.
20. Janinis J, Papadakou M, Xidakis E, *et al*. Combination chemotherapy with docetaxel, cisplatin, and 5-fluorouracil in previously treated patients with advanced/recurrent head and neck cancer: a phase II feasibility study. *Am J Clin Oncol* 2000, **23**, 128–131.
21. Janinis J, Papadakou M, Panagos G, *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**, 227–231.
22. Catimel G, Verweij J, Mattijssen V, *et al*. Docetaxel (Taxotere): an active drug for the treatment of patients with advanced squamous cell carcinoma of the head and neck. EORTC Early Clinical Trials Group. *Ann Oncol* 1994, **5**, 533–537.
23. Posner MR, Lefebvre JL. Docetaxel induction therapy in locally advanced squamous cell carcinoma of the head and neck. *Brit J Cancer* 2003, **88**, 11–17.
24. Colevas AD, Adak S, Amrein PC, *et al*. A phase II trial of palliative docetaxel plus 5-fluorouracil for squamous-cell cancer of the head and neck. *Ann Oncol* 2000, **11**, 535–539.
25. Gedlicka C, Formanek M, Selzer E, *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**, 145–150.
26. 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**, 845–849.
27. Posner MR, Glisson B, Frenette G, *et al*. Multicenter 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**, 1096–1104.
28. Colevas AD, Busse PM, Norris CM, *et al*. Induction chemotherapy with docetaxel, cisplatin, fluorouracil, and leucovorin for squamous cell carcinoma of the head and neck: a phase I/II trial. *J Clin Oncol* 1998, **16**, 1331–1339.
29. Vermorken JB, Remenar E, Van Herpen J, *et al*. Standard cisplatin/infusional 5-fluorouracil (PF) vs docetaxel plus PF (TPF) as neoadjuvant chemotherapy for non-resectable locally advanced squamous cell carcinoma of the head and neck: a phase III trial of the EORTC Head and Neck Cancer Group (EORTC 24971). *Proc Am Soc Clin Oncol* 2004, **22**. [abstract 5508].
30. Schoffski P, Catimel G, Planting AS, *et al*. Docetaxel and cisplatin: an active regimen in patients with locally advanced, recurrent or metastatic squamous cell carcinoma of the head and neck. Results of a phase II study of the EORTC Early Clinical Studies Group. *Ann Oncol* 1999, **10**, 119–122.