

Adjuvant Docetaxel, Cisplatin and 5-Fluorouracil (TPF) in Locally Advanced Squamous Cell Carcinoma of the Head and Neck

MEHRAN BAGHI, MARKUS HAMBEK, ANGELIKA MAY, ANDREAS RADELOFF, WOLFGANG GSTOETTNER and RAINALD KNECHT

Department for ENT- Surgery, University of Frankfurt am Main, Germany

Abstract. *Background:* In this phase II study, the efficacy and toxicity of a triple chemotherapy with docetaxel, cisplatin and 5-Fluorouracil (TPF) was evaluated in the adjuvant therapy of locoregionally advanced cancer of the head and neck. This represented the first use of polychemotherapy as single adjuvant therapy after surgery. *Patients and Methods:* Twenty patients with stage II-IV (UICC) squamous cell carcinoma of the head and neck (SCCHN) were treated by surgery of the primary and the regional lymph nodes. Four weeks after surgery, all patients received polychemotherapy consisting of docetaxel 75 mg/m² day 1, cisplatin 100 mg/m² day 1 and 5-Fluorouracil (5-FU) 1000 mg/m² days 1 through 4 (total dose 4000 mg/m²), on days 1, 2, 2 and 43 for a maximum of 3 cycles. The performance status of all patients at the beginning of the chemotherapy was 0-1 according to the Eastern Cooperative Oncology Group (ECOG). *Results:* Fifty-eight cycles were administered to the 20 patients. The major acute toxicities were mucositis (2 patients) and febrile neutropenia (4 patients). One patient dropped out after the first cycle because of severe mucositis. After a median follow-up of 16.5 months (range, 1-41 months), the median time to progression was 20 months (range, 16-22 months). The estimated overall survival according to Kaplan-Meier at the median time of follow-up was 90%. No distant metastases were detectable after the adjuvant chemotherapy with TPF in locally advanced SCCHN, neither were late effects observed. *Conclusion:* TPF was tolerated, with an acceptable toxicity profile, in patients with a good performance status. The preliminary results appear to justify further investigations to evaluate the efficacy of this modality in the adjuvant setting.

Correspondence to: Rainald Knecht, MD, Ph.D., ENT Department of Johann Wolfgang Goethe University Clinic, Theodor Stern Kai 7, 60590 Frankfurt am Main, Germany. Tel: +49-69-63014471, Fax: +49-69-63017710, e-mail: knecht@em.uni-frankfurt.de

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Patients with a locally advanced, resectable squamous cell carcinoma of the head and neck (SCCHN) have a poor prognosis. Even after radical surgery with postoperative chemoradiotherapy, most patients develop locoregional recurrence or distant metastasis. The rationale that justifies testing adjuvant chemotherapy in patients with locally advanced resected high-risk SCCHN is based on the following observations, as reported by Bernier *et al.* (1, 2): i) Even if 70%-75% of these patients remain free of disease at 2 years, the long-term prognosis of high-risk patients is poor. Only one-third of them are alive at 5 years. ii) Recent phase II and III studies have suggested a high efficacy of a number of novel cytotoxic drugs against epithelial cell cancer. iii) The incidence of distant metastases and second primaries becomes a more significant problem when the local control rate increases.

Adjuvant treatments, including chemotherapy, seem to improve the outcome of patients with advanced SCCHN (3). Cisplatin- and 5-Fluorouracil- (5-FU) based treatment (PF) showed an improvement of survival and disease-free survival in patients with unresectable SCCHN when administered with definitive radiotherapy (4). Neoadjuvant treatment of resectable laryngeal and hypopharyngeal cancer with PF obviates the need for surgery without affecting survival (5-8). The standard induction regimen with PF has been associated with a complete response rate of about 30% in randomized trials. Following the observation that docetaxel (Taxotere) possesses significant single agent antitumor activity in SCCHN, a modification of PF to docetaxel, cisplatin and 5-FU (TPF) was made. Substantial data support the use of docetaxel combined with PF. Posner *et al.* reported a 93% remission rate after 3 cycles of TPF (9). Also, Janinis *et al.* (10), Schrijvers *et al.* (11) and Tsukuda *et al.* (12) reported high remission rates after 3 to 4 cycles of TPF.

TPF is a 4-day chemotherapy regimen consisting of docetaxel and PF with a shorter chemotherapy infusion time, which was demonstrated in a phase I/II protocol (7,

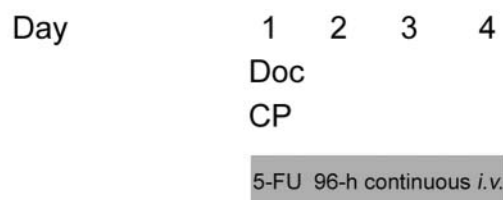


Figure 1. Administration schedule of adjuvant docetaxel (Doc), cisplatin (CP) and 5-Fluorouracil (5-FU) in patients with advanced squamous cell carcinoma of the head and neck. *i.v.*, intravenous infusion.

13) in the neoadjuvant setting. The 4-day regimen is an attempt to reduce the days of hospitalization and systemic toxicity, while maintaining efficacy (8).

Based on the accumulated evidence that the TPF regimen is more effective than the PF regimen, the efficacy and toxicity (phase II study) of this regimen was evaluated for the first time in the single adjuvant setting.

Patients and Methods

Objective. The primary objective of this phase II study was to evaluate the efficacy and the toxicity of a polychemotherapy with a triple regimen consisting of docetaxel, cisplatin and 5-FU in the adjuvant setting. A secondary objective was to observe the recurrence-free survival.

Inclusion and exclusion criteria. All patients had histologically-confirmed SCCHN of the head and neck. Surgery was performed in every patient 4 weeks before adjuvant polychemotherapy was initiated. All patients had Stage II- IV tumors, without evidence of distant metastasis, Eastern Cooperative Oncology Group (ECOG) performance status 0-1, WBC count of 3,000 or more cells/ μ l, platelet count of $\geq 100,000/\mu$ l, levels of hemoglobin(Hb) of 10 g/dl or more, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than or equal to 3.5 times the upper limit of normal (ULN), total bilirubin less than or equal to 1.25 times the ULN and creatinine less than or equal to 2.5 mg/dl. The patients were required to be able to tolerate 3l of intravenous (*i.v.*) normal saline per day. They were also required to be older than 18 years of age. Additional exclusion criteria included a current or past history of another serious medical condition, such as myocardial infarction, uncontrolled hypertension, diabetes mellitus, second malignant tumor, psychiatric disorders or active infection; pregnancy was also a criteria for exclusion.

Surgical treatment. All patients underwent primary tumor resection. Table II shows the type of surgical techniques. Neck dissection was performed in all patients. A bilateral neck dissection was performed when the tumor extended over the midline. The type of neck dissection depended on the primary tumor site and on tumor extension, as stated in Table II.

Treatment schedule and dose administration. All patients received either an intravenous (*i.v.*) Port system or a double- lumen

Table I. Patient and tumor characteristics.

No. of patients	20
Assessable	19
Age, (y)	
Median	59
Range	43-83
Sex	
Men	17
Women	3
Performance status (ECOG)	
0	10
1	10
Primary site of tumor	
Oral cavity	1
Oropharynx	6
Larynx	6
Hypopharynx	3
Cervical lymph node (CUP)	3
Parotid gland	1
Tumor grade (UICC)	
II	4
III	6
IV	10

ECOG, Eastern Cooperative Oncology Group.
CUP, carcinoma of unknown primary.
UICC, Union International Centre Cancer.

indwelling venous catheter, placed before the initiation of therapy to facilitate the drug and fluid administration. The chemotherapy regimen was applied as follows: 8 mg of oral dexamethasone, administered approximately 12 hours before and after docetaxel. One hour before administration of docetaxel, a dose of 16 mg *i.v.* dexamethasone was additionally administered. Docetaxel 75 mg/m² was administered *i.v.* in 250 ml normal saline over 1 hour on day 1. One hour after completion of docetaxel, cisplatin 100 mg/m² was also delivered on day 1. Finally 5-FU 1000 mg/m², on days 1 through 4 (total dose 4000 mg/m²), was delivered by continuous *i.v.* infusion at 1.5 to 2 times of body surface with normal saline. All patients received additional prophylactic oral antiemetics including 8 mg ondansetron *i.v.* every 8 hours beginning immediately before cisplatin infusion for the duration of the chemotherapy. Subcutaneous G-CSF (Neupogen[®]) was administered according to body weight (5 μ g/kg BW/ day) only in patients with an absolute neutrophil count less than or equal to 100 cells/ μ l until it recovered to the upper limit of normal (ULN). Oral ciprofloxacin 500 mg was also administered in this group of patients. Additional *i.v.* supplementation of electrolytes (*e.g.* potassium or magnesium) was given on an as-needed basis. The patients were also instructed to rinse the oral cavity several times daily with normal saline. The chemotherapy regimen was repeated every 21 days for a maximum of 3 cycles. Figure 1 shows the administration schedule. In the event of major toxicities, patients were admitted to the hospital.

Table II. *Type of surgical techniques.*

Type of resection	No. of patients
Transoral laser resection + SND	13
Laryngectomy + mRND	1
Laryngopharyngectomy + mRND	1
Partial laryngectomy + mRND	1
mRND in CUP patients	3
Total parotidectomy + mRND	1

SND, selective neck dissection.

mRND, modified radical neck dissection.

CUP, carcinoma of unknown primary.

Subsequent cycles could be delayed for up to 7 days if, on days 22 or 43, there was evidence of major toxicities. In case of ongoing toxicities, patients were hospitalized and were treated on an as-needed basis. A dose reduction of 25% to docetaxel 60 mg/m², cisplatin 75 mg/m² and 5-FU 750 mg/m² was performed for subsequent cycles in case of major toxicities. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 3.0 (NCI CTC).

Follow-up. The follow-up began 1-3 months after completion of the adjuvant chemotherapy. It included a clinical examination and ultrasound of the neck every 3 months during the first 3 years and every 6 months from 3 to 6 years. The follow-up also included an annual X-ray of the chest. In case of recurrence, magnet resonance imaging (MRI) of the neck and an endoscopic examination were performed.

Results

Toxicity. From June 2001 to December 2004, 20 patients were enrolled in this study. The baseline patient characteristics are shown in Table I. Fifty-eight adjuvant cycles of TPF were administered. Nineteen patients received 3 cycles of TPF. There were no treatment-related delays in therapy in these 19 patients. The cycles were administered on days 1, 22 and 43. Toxicity was assessed in all patients. The side-effects are listed in Table III.

Five patients had to be hospitalized because of major toxicity grade IV according to NCI CTC. Four patients were admitted for febrile neutropenia (temperature 38°C and absolute neutrophil count less than 500 cell/μl) and were treated with *i.v.* ciprofloxacin, 400 mg twice daily. One of these 4 patients remained hospitalized for more than 3 weeks because of additional grade IV mucositis and problems with nutrition. This patient was 83 years old but in good general health (ECOG 1) before the start of treatment. The adjuvant TPF was discontinued in this patient, who dropped out after 1 cycle. All patients with febrile neutropenia received subcutaneous G-CSF according to their body weight until the absolute neutrophil increased

Table III. *Acute toxicities grades 3 or 4 with TPF.*

Toxicity	No. of patients
Anorexia	1
Febrile neutropenia	4
Mucositis	2
Renal failure	1
Anemia	3
Electrolyte disorder	1

to the ULN. One patient was admitted because of mucositis grade IV according to NCI CTC. This patient was also treated with subcutaneous G-CSF and broad-spectrum antibiotics. Additionally, he received local mucosa treatment. One patient developed grade III renal failure after the third cycle, which was reversible after continuous administration of 3l normal saline over 5 days. The most common non-hematological toxicities associated with TPF included alopecia and mucositis. Alopecia was total but reversible. There were no episodes of thrombocytopenia. One patient showed an electrolyte disorder grade III according to NCI CTC. He was treated with *i.v.* potassium and magnesium. No patient developed a late effect after adjuvant TPF.

Outcome. Overall, 19 out of the 20 patients with positive nodal status, whose primary tumor sites and neck nodes had been resected, underwent the adjuvant TPF regimen consisting of 3 cycles. One patient received 1 cycle. This patient, with a SCC of the parotid gland, did not tolerate the adjuvant TPF because of major toxicity (mucositis grade IV) and had to be excluded from the study. No patient was treated with adjuvant radiotherapy. Thirteen out of the 20 patients had been operated with microscopically-safe resection margins. Seven out of the 20 patients showed microscopic-positive resection margins, 3 of them demonstrating a relapse. In 1 patient salvage total laryngectomy was performed. The other patient, who was recommended a salvage operation, rejected total laryngectomy and radiation. He then received chemotherapy. The third patient showed submucosal infiltration of the esophagus after removal of the larynx (in fresh-frozen sections). The primary was not totally resectable. He showed progression 16 months after the adjuvant TPF had ended, whereafter he also received chemotherapy. The median follow-up was 16.5 months (range, 1-41 months). The median time to progression in 3 patients was 20 months (range, 16-22 months), while 16 out of 19 patients are tumor-free. The estimated overall

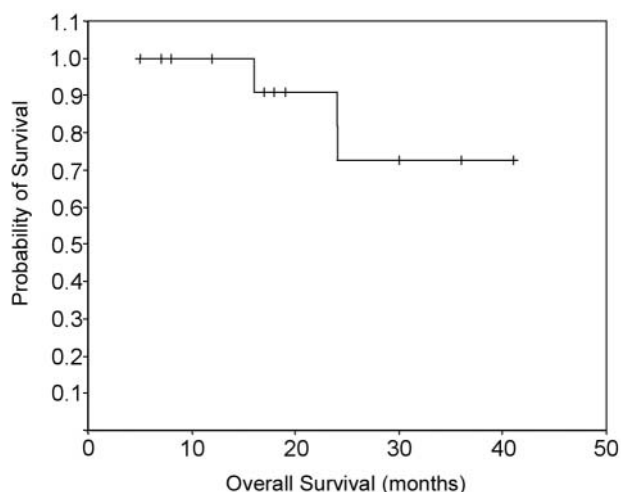


Figure 2. Kaplan- Meier overall survival curve.

survival, according to Kaplan-Meier, at the median time of follow-up (16.5 months) was 90% (see Figure 2).

Discussion

The standard treatment for advanced head and neck cancer comprises a multidisciplinary approach, including surgery and chemoradiotherapy. The role of chemotherapy in the adjuvant management of head and neck cancer remains a subject of continuous debate. The combination of cisplatin and 5-FU with radiotherapy was shown to give high response rates in untreated patients (1, 6, 14). Meta-analyses of phase III trials, which tested the addition of chemotherapy to radiation therapy in the adjuvant setting, suggested that the use of chemotherapy offers a survival advantage (10). This beneficial effect is associated with increased toxicity and mandates more supportive care and physician experience for successful delivery. It is interesting to note that randomized trials seem to show only a marginal antitumor activity of chemotherapy in combination with radiotherapy at distant sites (14). The addition of chemotherapy during radiation contributes to higher rates of toxicity, making the application of full-dose chemotherapy not possible in combination with radiation. Consequently, higher rates of distant metastases and second primaries result.

The recent emergence of the taxanes, with promising results as single agents against SCCHN, has prompted researchers to define the role of taxane-based combination chemotherapy in the combined modality treatment of locally advanced SCCHN. Some agents, such as hydroxyurea, work only through radiation sensitization, whereas the taxanes

work by both sensitization and direct antitumor activity. The antitumor activity of the taxanes seems to be independent of their sensitization mechanism (15, 16). Unfortunately, they promote a significant normal tissue sensitization to radiotherapy, so that chemoradiotherapy with taxanes is associated with a brisker local reaction than with radiotherapy alone (17, 18). Thus, it seems to be important to evaluate the efficacy of combined chemotherapy alone in the adjuvant setting.

Docetaxel (Taxotere) is a new agent that has demonstrated significant activity against SCCHN (18). A number of phase I/II studies have explored the combination of docetaxel, cisplatin and 5-FU in SCCHN, (2, 8, 12) with promising results. Attempts have been made to shorten the duration of the 5-FU infusional therapy from the standard 5-day infusion to a 4-day infusion, in an effort to reduce the days of hospitalization and systemic toxicity, while maintaining efficacy (19).

In this phase II study, TPF was introduced for the first time as single adjuvant therapy after surgery. We chose 20 patients with a good performance status equal to or less than 1 according to ECOG. All the patients were treated by surgery and underwent a triple regimen with docetaxel 75 mg/m² day 1, cisplatin 100 mg/m² day 1 and 5-FU 1000 mg/m² days 1 through 4, as shown in Figure 1. This regimen was repeated for a maximum of 3 cycles on days 1, 22 and 43.

Treatment-related toxicity is a major concern in combined modality approaches. A major disadvantage of concomitant chemoradiation is toxicity (10), which causes treatment interruption. Wendt *et al.* reported a 38% rate of grade III or IV mucositis for concomitant chemoradiation (20). In our study, the major toxicity was febrile neutropenia (20%) grade 3-4 according to NCI CTC. A grade 3-4 mucositis was seen in 10% of patients. It is possible that the mild rate of mucositis in our patients was because of the shorter duration of infusion of 5-FU (4 versus 5 days), as reported by Janinis *et al.* (10). Thus, the low rate of mucositis makes this regimen attractive for further investigations. There were no treatment-related deaths from this regimen. All other major toxicities were reversible. One patient was excluded after the first cycle because of grade 4 mucositis. No late effects were observed.

In the majority of patients with head and neck carcinoma the disease is locally advanced (Stage III-IV) at presentation. The standard therapy for such patients, consisting of surgery and adjuvant radiation or chemoradiation, shows a cure rate that does not exceed 30% (3, 4). Further, Bernier *et al.* reported a 15-20% rate for patients developing distant metastasis treated with the standard chemoradiation (1).

No patient developed distant metastasis during the observation period. In 3 out of 7 patients with positive pathological margins, TPF adjuvant chemotherapy did not

contribute to complete remission. This underlines the need for surgical resection in the case of positive margins, as with adjuvant radiotherapy or chemoradiotherapy.

Our data suggest that TPF chemotherapy is a feasible systemic treatment option in the adjuvant setting in patients with locally advanced head and neck cancer. The low rate of major toxicities makes this regimen suitable for patients with a compromised performance status. Further investigation will prove the efficacy of this therapeutic option in patients with locally advanced SCCHN, comparing it with adjuvant standard radiotherapy/ radiochemotherapy in terms of local control, survival and toxicity.

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