Gemcitabine and paclitaxel in metastatic or recurrent squamous cell carcinoma of the head and neck: a phase I–II study

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The purpose of this study was to determine the maximum tolerated dose, toxicity profile and anti-tumor activity of paclitaxel in combination with gemcitabine when administered to patients with unresectable locally recurrent or metastatic squamous cell carcinoma of the head and the neck (SCCHN). Twenty-seven patients were treated in a phase I–II study with gemcitabine at a dose of 800 mg/m^2 on days 1 and 8, escalating to a dose of 1000 mg/m^2, plus escalating doses of paclitaxel (100, 135 and 175 mg/m^2) on day 2. Treatment consisted of 6 cycles repeated every 3 weeks. The main toxicity was myelosuppression. Other toxicities were mild and manageable. Due to grade 4 neutropenia at higher doses the recommended dose level of the gemcitabine/paclitaxel combination was 1000/135 mg/m^2. Four patients achieved a partial response and no patient had a complete remission, giving an overall response rate of 14.8%. The median time of survival was 24 weeks. We conclude that the combination of paclitaxel and gemcitabine is tolerated, but shows insufficient clinical activity in patients with recurrent and/or metastatic SCCHN to warrant further testing. ***Anti-Cancer Drugs*** **16:1115–1121 © 2005 Lippincott Williams & Wilkins.**

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Introduction

Squamous cell cancer of the head and the neck (SCCHN) is the sixth most common cancer worldwide, and the third most common cancer among men in developing countries [1]. Men are at higher risk of developing these cancers and are affected 1–3 times more often than women in industrialized countries. The estimated number of new cases of SCCHN is over 60 000 per year in western countries [2]. Most SCCHN cases are locally advanced at presentation, with up to 75% of patients having stage III–IV, M0 disease [3,4]. Stage of disease at diagnosis is regarded as the single most important prognostic factor [5]. The 5-year survival rate ranges from 20 to 50% and 10 to 30% for stage III and IV SCCHN, respectively. Stage I–II SCCHN is often curable with either surgery or radiotherapy, but it is generally accepted that treatment of locally advanced SCCHN should involve a combined modality approach [5].

Patients with recurrent or metastatic disease receive chemotherapy, but the objective response rate is about 10–50% for single-agent treatments, with a short response duration ranging from 4 to 6 months. Proven effective drugs in SCCHN are cisplatin, 5-fluorouracil (5-FU), methotrexate, bleomycin, carboplatin and ifosfamide. Controlled studies have established cisplatin and continuous infusion 5-FU as the standard regimen for unresectable locally advanced SCCHN patients [6–9]. Cisplatin-containing regimen are the most widely used and produce an overall response rate in the range of 30–35% in the treatment of recurrent or metastatic diseases. Combination chemotherapy produces higher response rates than single agents, but median survival does not exceed 6 months in either case [10,11].

Taxanes have been recently introduced in the treatment of SCCHN. Paclitaxel and docetaxel have shown significant activity in patients with SCCHN [12,13]. Taxoids act to promote tubulin polymerization and the formation of stable microtubules. The microtubules produced in the presence of taxoids are resistant to disassembly by physiologic stimuli and cells exposed to these agents exhibit an accumulation of disorganized microtubule arrays [14]. In a single-agent phase II study conducted by the Eastern Cooperative Oncology Group (ECOG), paclitaxel at a dose of 250 mg/m^2 over 24 h produced an overall response rate of 40% [12], whereas other studies with paclitaxel at a dose of 175–250 mg/m^2 showed an overall response rate of 20–35% [15,16]. A direct comparison in a randomized phase II study showed overlapping 95% confidence intervals (CIs) of the

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response rates obtained by standard-dose methotrexate and two infusion schedules of paclitaxel in patients with recurrent and/or metastatic head and neck cancer [17].

Gemcitabine is attractive for combination chemotherapy due to its multiple mechanisms of action and mild toxicity profile at an active dose. Gemcitabine acts by incorporation of its triphosphate (dFdCTP) into DNA, subsequently leading to inhibition of exonuclease and DNA repair. Several self-potentiating mechanisms have been described, enhancing the incorporation of dFdCTP into DNA and possibly also into RNA [18–20]. Most phase II studies have been performed utilizing a weekly × 3 schedule, repeated every 4 weeks, with short-lived myelosuppression being the dose-limiting side-effect and maximum tolerated doses (MTDs) ranging from 790 to 1370 mg/m^2/week [21–23]. Hepatic liver dysfunction is characterized by an increase of the level of transaminase enzymes, but it is usually mild, non-cumulative and infrequently requires treatment discontinuation. Experience with the use of gemcitabine in advanced SCCHN is limited. In a phase II trial the drug was given initially at a dose of 800 mg/m^2 weekly in patients who had previously undergone chemotherapy. In that study the dose was increased to 1250 mg/m^2 in chemotherapy-naive patients. The overall response was 13% [24]. In a phase II trial of the Southwest Oncology Group, 26 patients with recurrent or metastatic SCCHN were registered to receive a dose of 1250 mg/m^2 weekly [25]. In this study, no objective treatment response (95% CI 0–13%) could be observed, with a median survival of 6 months in this highly resistant disease population, suggesting insufficient clinical activity as monotherapy in the treatment of SCCHN.

The disappointing results of single-drug therapy with gemcitabine have led to testing chemotherapy combinations. In-vitro studies showed either cross-resistance or collateral sensitivity in resistant tumor cell lines, identifying taxanes and gemcitabine as probably suitable drug partners [26,27]. The combination of paclitaxel and gemcitabine was then tested in 37 patients with solid tumors [28]. Dose-limiting toxicity (DLT) was not seen at doses of 150 mg/m^2 of paclitaxel and 3000 mg/m^2 of gemcitabine biweekly. Hematologic toxicities were grade 4 neutropenia and thrombocytopenia in a minority of patients. Only grade 3 mucositis and asthenia were reported as non-hematological toxicities. A combination chemotherapy of paclitaxel and gemcitabine was then tested in a variety of tumors, e.g. non-small cell lung cancer (NSCLC), metastatic breast cancer and other solid tumors, with comparable responses to established therapy regiments and low toxicities [29–38]. Just one study has been published testing the combination of paclitaxel and gemcitabine in SCCHN. In a phase II study conducted by the Hellenic Cooperative Oncology Group, 44 patients with recurrent or metastatic head and neck cancer were given first-line therapy with paclitaxel 200 mg/m^2 day 1 and gemcitabine 1000 mg/m^2 day 1 and 8 every 3 weeks. Grade 3 and 4 toxicities included neutropenia (21%), thrombocytopenia (5%), anemia (5%), infection (5%), flu-like symptoms (5%) and peripheral neuropathy (2%). The overall response rate was 41%, with 11% of patients achieving a complete response and a median survival of 9 months [39].

In the present study we evaluate the tolerability and clinical efficiency of a combined chemotherapy with paclitaxel and gemcitabine in patients with recurrent or metastatic SCCHN.

Material and methods

Patient eligibility

Patients enrolled in this study were required to have a histologically proven SCCHN that was metastatic, or had persisted or recurred following definitive surgery and/or radiation therapy. Eligibility criteria included age 18–75 years; performance status ≤ 2 according to the scale of the Eastern Cooperative Oncology Group (ECOG) with a Karnofsky index of $\geq 70\%$; life expectancy of >12 weeks; adequate bone marrow function with absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l and hemoglobin ≥ 90 g/l; adequate renal function with a serum creatinine $\leq 1.25 \times$ institutional upper limit of normal (ULN); adequate liver function with a serum bilirubin $\leq 1.25 \times$ institutional ULN. Patients with a second malignancy except curable basalioms and adequately treated carcinoma *in situ* of the cervix, as well as woman who were pregnant or nursing, patients with cardiac arrhythmias or cardiac failure, patients with polyneuropathy $\geq$grade 2 according to the WHO scale, or patients with acute infections were excluded from the study. All patients provided written acknowledgments of informed consent in accordance with institutional and federal guidelines, which was approved by the ethical review board of the institution.

Pretreatment evaluation included medical history and clinical examination, including performance status, length and weight. In addition, hematology and blood chemistry tests, and ECGs and chest X-rays were performed. To assess the extent of the disease ultrasound of the abdomen, computed tomography or magnetic resonance imaging scans were performed.

Study design

The primary objective of this study was to determine the MTD of gemcitabine/paclitaxel combination therapy, followed by a phase II study to determine the toxicity profile and anti-tumor activity. Four patients received an initial dose level of gemcitabine as a 800 mg/m^2 i.v. infusion over 30 min on day 1 and 8, and paclitaxel as a 135 mg/m^2 i.v. infusion over 3 h on day 2 (dose level 0)

with standard premedication (dexamethasone 2×20 mg p.o., clemastine 2 mg i.v. and cimetidine 300 mg i.v.). Treatment was repeated every 3 weeks. Complete blood cell counts and serum creatinine were measured weekly, and complete blood chemistry was performed before each treatment cycle. Toxicity was defined by criteria of the WHO. In the absence of non-hematologic toxicities grade III/IV (except of alopecia and vomiting), a dose escalation for gemcitabine to dose level 1 as a 1000 mg/m^2 i.v. infusion on day 1 and 8 was performed, and all further patients treated with this dosage. A dose escalation for paclitaxel was performed in accordance with the following scheme: level 1: paclitaxel 135 mg/m^2, gemcitabine 1000 mg/m^2; level 2: paclitaxel 175 mg/m^2, gemcitabine 1000 mg/m^2. The dose escalation for paclitaxel was performed for an ANC $\geq 1 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l and neuropathy grade < 3 according to WHO criteria prior to the next cycle of chemotherapy.

Dosage modifications were performed for hematologic and non-hematologic toxicities. Paclitaxel dosage was reduced for an ANC $< 0.5 \times 10^9$/l for more than 7 days or an ANC $< 0.1 \times 10^9$/l for more than 3 days. Alternative, granulocyte colony-stimulating factor use was allowed in patients who had experienced grade III or IV neutropenia during a prior treatment cycle. For non-hematologic grade III or IV toxicity (except nausea, vomiting and alopecia), a dosage reduction of one dose level was employed in subsequent drug doses. Treatment was discontinued at disease progression, unacceptable toxicity, a treatment delay of more than 2 weeks or patient wish to stop the therapy. Usually, 6 cycles were given to responding patients or patients with stable disease. Patients with a complete remission received a further 2 cycles. Patients were followed for at least 3 weeks after the last drug dose and until recovery of all toxic effects.

Statistical design and response assessment

A response probability of 30% or greater would have been of interest, while further testing would not be pursued if the response probability was 20% or lower. A two-stage design was used [40] for patient accrual, with 18 eligible patients required for the first stage. If at least three responses had been observed, 36 additional eligible patients would have been accrued to the second stage. This design had a significance level of 5% (probability of falsely declaring an agent with a 5% response probability for warrant further study) and a $1-\beta$ error of 20% (probability of correctly declaring an agent with a 20% response probability to warrant further study). Response to therapy was assessed according to WHO criteria every 3 cycles. Complete response was defined as the complete disappearance of all tumor lesions for at least 4 weeks. Partial response was defined as a reduction of 50% or more in the product of the largest diameters of the lesions while no new lesions as determined by two observations not less than 4 weeks apart. Stable disease was defined as less than 50% decrease and less than 25% increase in the sum of the product of the largest diameter of all measurable lesions with no appearance of new lesions. All other patients were considered to have a progressive disease. Duration of overall survival was calculated from day 1 of the first drug administration to death using the Kaplan–Meier method.

Results

Twenty-seven patients with a SCCHN were accrued to this trial between October 1997 and April 2002. All of them were assessable for response, and could be included in the toxicity and response analysis. Of these patients, two completed 1 cycle of treatment, one had 2 cycles of treatment and 24 completed 3 or more cycles of treatment. The patient demographics included a median range of 58.4 years (range 41–70) (Table 1). There was an expected male predominance (24 men, three women). The ECOG performance status was 0–1 for 25 patients and 2 for two patients. Sixteen patients (59%) received a combination of surgery and radiotherapy prior to the study, whereas one patient (4%) had previously been treated just by radiotherapy and two (7%) patients by surgery alone. Four patients (15%) had received a prior therapy with surgery and combined radio-chemotherapy. Three patients had not been treated before.

The first four patients were treated with gemcitabine 800 mg/m^2 and paclitaxel 135 mg/m^2 (level 0). The absence of non-hematologic toxicities grade 3 or 4 in

Table 1 Patient and tumor characteristics

	n
Patients enrolled	27
Age (years) [median (range)]	58.4 (41–70)
Sex	
male	24
female	3
Performance status (ECOG)	
0	9
1	16
2	2
3	0
4	0
Primary site of the tumor	
larynx	5
oropharynx	7
hypopharynx	5
floor of the mouth	2
tongue	2
paranasal sinuses	1
cancer of unknown primary	1
oro-, hypopharynx	1
oro-, hypopharynx, larynx	1
oropharynx, larynx	1
cavity of the mouth, larynx	1
squamous cell carcinoma histology type	27
Primary treatment	
surgery	2
radiotherapy	1
surgery and radiotherapy	16
surgery, radiotherapy and chemotherapy	4
no previous treatment	3

these patients enabled us to perform the further cycles with dose levels 1–2. Nineteen patients (70%) received the chemotherapy at dose level 1 with gemcitabine 1000 mg/m^2 and paclitaxel 135 mg/m^2, and three patients (11%) at dose level 2 with gemcitabine 1000 mg/m^2 and paclitaxel 175 mg/m^2. In five patients, the dose had to be reduced due to hematologic toxicities (four patients with grade 4 leukopenia) and stomatitis (two patients with grade 3), three patients from level 1 to level 0 and two patients from level 2 to level 1. In one patient who received dose level 2, the treatment was discontinued after the first cycle because of progressive disease. Therefore, none of the patients tolerated the treatment with dose level 2. Ten patients (37%) completed all 6 cycles of treatment and 14 patients (52%) received 4 cycles or more of treatment. The treatment was discontinued because of progression of disease in 17 patients, early death in none, voluntary withdrawal in one and hematologic or non-hematologic toxicities in none of the patients. See Table 2.

Myelotoxicity was the most important toxicity of the gemcitabine/paclitaxel combination. Table 3 summarizes the hematologic toxicities of the first treatment cycle. Overall, grade 3–4 leukopenia was observed in 15 out of 27 patients (56%), whereas no patient had a grade 3–4 thrombocytopenia or anemia. After the sixth cycle of treatment two patients (20%) developed a grade 3–4 leukopenia and one patient (10%) developed a grade 3 anemia. The lower rate of hematologic toxicities after the sixth cycle in comparison to the first cycle may be due to a positive selection during the course of chemotherapy for patients with a better hematologic capacity.

The incidence of non-hematologic toxicities like nausea and vomiting was low. Considering prophylactic treatment with 8 mg ondansetron on day 2 of each cycle, nausea and vomiting were infrequent and mild to moderate. In the first treatment cycle, 10 patients (37%) had grade 1–2 nausea and vomiting, two patients had developed a grade 3 diarrhea and two patients had developed grade 3 stomatitis/mucositis. Some particular gemcitabine-related toxicities, such as elevated liver enzymes and flu-like syndrome, were mild [only grade 1–2 toxicities in four patients (15%) in the first cycle]. In the second and third treatment cycle, grade 3 pulmonary events and grade 3 cardiac events occurred in two cases each. Grade 1–2 nausea and vomiting was observed in patients in each cycle. Overall, during the first 3 cycles, 20 grade 3–4 non-hematologic toxicities occurred out of 76 treatment cycles (26%), and during cycles 4–6, 10 grade 3–4 non-hematologic toxicities were observed out of 36 cycles (27%).

Table 2 Selected treatment characteristics: dosage of chemotherapy and courses delivered per patient (a total of 112 courses were delivered)

	Dose level	Paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)	No. patients
	0	135	800	5
	1	135	1000	19
	2	175	1000	3
Dosage reduced	1→0			3
	2→1			2
No. cycles per patient				
1				2
2				1
3				10
4				2
5				2
6				10

Table 3 Overall toxicities (number of cycles, a total of 112 courses were delivered)

	CTC grade			
	1	2	3	4
Hematologic				
anemia	51	25	4	0
leucopenia	13	28	27	13
neutropenia	17	16	19	24
thrombocytopenia	8	2	1	0
Non-hematologic				
nausea and vomiting	11	8	3	0
diarrhea	2	1	2	0
obstipation	3	5	0	0
stomatitis/mucositis	4	10	2	0
skin	1	2	0	0
infections	4	3	0	0
fever	2	4	0	0
alopecia	4	16	9	0
pain	7	27	0	0
pulmonary events	3	0	4	0
cardiovascular events	5	1	2	0
consciousness	2	0	0	0
AST/ALT elevation	9	7	0	0

Objective response was observed in four of the 27 evaluable patients (14.8%) (Table 4). All four patients achieved a partial response, whereas none of the patients had a complete remission. One of these patients was treated with dose level 0, two patients with dose level 1 and one patient with dose level 2. In two patients, the dose level had to be reduced due to stomatitis grade 3 and leukopenia grade 4 (one patient dose level 2 to 1, one patient 1 to 0). Twenty-one out of 26 assessable patients had developed progressive disease under treatment and one patient achieved a stable disease. Of these patients, 12 developed a progressive disease within the first 3 cycles of treatment, whereas five patients showed a tumor progression after the sixth cycle of treatment. The median survival was 24 weeks (168 days, Fig. 1). With an achieved response probability of less than 20% with 27 eligible patients, the study was not pursued in accordance with the statistically evaluated defaults prior to evaluation.

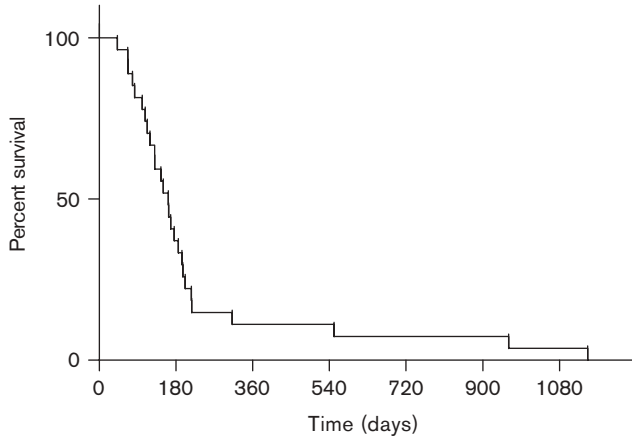
Discussion

The primary goal of this study was to determine the MTD, toxicity profile and anti-tumor activity of

Table 4 Tumor response

Response	No. patients	(%)
Complete remission (CR)	0	0
Partial remission (PR)	4	14.8
Stable disease	1	3.7
Progressive disease	21	77.8
No evaluation	1	3.7
Overall response (CR + PR)	4	14.8

Fig. 1



Overall survival in patients with recurrent or metastatic SCCHN following treatment with gemcitabine and paclitaxel.

gemcitabine/paclitaxel combination chemotherapy in the treatment of patients with SCCHN. As single agents, both gemcitabine and paclitaxel have demonstrated a broad spectrum of clinical anti-tumor activity with favorable toxicities profiles. The combination of these agents is promising based on the achieved dose intensity, toxicity profile and observed anti-tumor activity in different tumors. Treatment schedules with gemcitabine and paclitaxel have been evaluated in several phase I–II clinical trials. In NSCLC, Giaccone *et al.* [29] conducted a phase I/II study with escalating doses of paclitaxel 150–200 mg/m^2 on day 1 and a fixed dose of gemcitabine 1000 mg/m^2 on day 1 and 8 in a 3-week schedule. The combination was well tolerated and the mild toxicities allowed an increase of the paclitaxel doses to 200 mg/m^2. The main toxicity was myelosuppression with a minimal incidence of grade 3 or 4 neutropenia (17%). On the basis of this, the European Organization for Research and Treatment of Cancer Lung Cancer Group conducted a phase III study using paclitaxel 175 mg/m^2 day 1 and gemcitabine 1250 mg/m^2 day 1 and 8 every 3 weeks [30]. Other trials used similar doses of paclitaxel and gemcitabine in the first-line treatment of NSCLC [31,33–35]. The DLTs in each case were myelosuppression with grade 3–4 neutropenia (8.9–30% of the patients) and less frequent thrombocytopenia or anemia. Non-hematologic toxicities were relatively mild, with few or no cases of grade 3 toxicities. In patients with solid malignancies, a phase I study by Fleming *et al.* [32] recommended a dose of 900 mg/m^2 gemcitabine (day 1 and 8) along with 150 mg/m^2 paclitaxel (day 1) every 3 weeks. Rothenberg *et al.* [28] used a 2-week schedule in patients with refractory solid tumors. The MTD was reached with doses of paclitaxel at 150 mg/m^2 and gemcitabine at 3000 mg/m^2, with DLTs being neutropenia and a severe increase of transaminases. In phase I–II studies in pre-treated NSCLC patients, gemcitabine and paclitaxel were used in reduced doses with 900–1000 mg/m^2 gemcitabine and 150–200 mg/m^2 paclitaxel [36,37]. All of these studies with the combination of paclitaxel and gemcitabine have repeatedly shown the principal DLT to be grade 4 neutropenia.

The optimal dose for paclitaxel in combination with gemcitabine in the treatment of patients with metastatic or recurrent SCCHN has been defined in the present study as 135 mg/m^2 paclitaxel (day 2) and 1000 mg/m^2 gemcitabine (day 1 and 8) (dose level 1). However, our study showed a higher hematologic toxicity (56%) than in previous studies. Furthermore, a dose escalation to 175 mg/m^2 paclitaxel was not tolerated due to increased hematologic toxicities. All three patients who had received the chemotherapy in dose level 2 developed a dose-limiting myelotoxicity with grade 4 neutropenia. Two patients could continue the therapy with a reduced dose, whereas in one patient the treatment had to be interrupted due to disease progression. A comparable study in the treatment of patients with advanced SCCHN by Fountzilas *et al.* [39] used 1100 mg/m^2 gemcitabine on day 1 and 8 followed by 200 mg/m^2 paclitaxel on day 1 in a 3-week schedule. This therapy using higher doses of agents was tolerated very well with a lower incidence of grade 3–4 toxicities in comparison to our study. The higher rate of hematologic toxicities and the lower tolerated dose of agents observed in our study is most likely due to the fact that 24 (89%) of our patients had already received therapy (surgery, radiotherapy and/or chemotherapy) prior to this study, whereas in the study by Fountzilas *et al.* [39] and others chemotherapy-naive patients or patients with just one prior regime were accrued. The non-hematologic toxicities observed in our study were relatively mild and similar to the observations in other studies. Two patients developed grade 3 stomatitis and two patients developed grade 3 diarrhea, which made dose reduction necessary. Pneumonitis did not occur and the hepatotoxic effects were relatively mild (no grade 3 or 4 toxicity).

We could achieve an overall response rate of only 14.8% in the present study, which was lower than the expected probability of 20% necessary to continue the study due to the statistic evaluated defaults prior to evaluation,

according to the Simon statistical analysis of the two-stage approach [40]. The response rate achieved in the present study is lower than the response rate achieved in studies investigating a combination therapy with paclitaxel and gemcitabine as well as single-agent paclitaxel in SCCHN. In the study conducted by Fountzilas *et al.* [39], an overall response rate of 41% could be achieved with slightly higher doses than in our study with 1100 mg/m^2 gemcitabine (day 1 and 8) and 200 mg/m^2 paclitaxel, which could be partially attributable to patient selection. However, studies analyzing the effect of single-agent paclitaxel also reported overall response rates of 20–40%, although with limited patient numbers (17–30) [12,15,16], whereas single-agent chemotherapy with gemcitabine failed to show any significant clinical activity in advanced SCCHN [24,25]. Of note, the combination of gemcitabine with the highly effective cisplatin also revealed just a discrete activity in patients with advanced SCCHN, showing a response rate of 22.7% [41].

From our study and the results of these latter studies we conclude that combination therapy with paclitaxel and gemcitabine as well as single-agent gemcitabine does not yield sufficient clinical activity to warrant further testing in SCCHN. Other combination chemotherapies of paclitaxel with, for example, cisplatin showing higher response rates [42–45] should be favored, although at the expense of higher toxicities leading to dose limitations in patients with advanced SCCHN due to previous treatments of the tumor and comorbidity. Further investigations of other chemotherapy combinations with tolerable toxicities are needed in the treatment of metastatic and recurrent SCCHN.

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