Phase II study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck

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Background: The efficacy and safety of a novel combination of weekly paclitaxel and the epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab for the first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck were investigated.
Patients and methods: Patients received paclitaxel (80 mg/m²) and cetuximab (400/250 mg/m²), weekly, until disease progression or unacceptable toxicity. The primary end point was response rate.

Results: Among 46 patients enrolled, the overall response rate was 54% [95% confidence interval (CI) 39% to 69%], with 10 (22%) complete responses and a disease control rate of 80%. Median progression-free and overall survival times were 4.2 (95% CI 2.9–5.5 months) and 8.1 months (95% CI 6.6–9.6 months), respectively. Common grade 3/4 adverse events were acne-like rash (24%), asthenia (17%) and neutropenia (13%). Prior chemotherapy and the development of acne-like rash were associated with tumor response but not survival. No association between tumor EGFR expression or EGFR gene copy number and response or survival was found.

Conclusion: The combination of cetuximab and weekly paclitaxel was active and well tolerated by these poor prognosis patients and may be an option for the treatment of medically unfit patients, particularly those for whom platinum is contraindicated.

Key words: cetuximab, head and neck, metastatic, paclitaxel, recurrent, squamous cell carcinoma

Introduction

Squamous cell carcinoma of the head and neck (SCCHN) represents 4% of all cancers diagnosed worldwide, with >500 000 new cases diagnosed and over 300 000 attributable deaths recorded in 2008 [1]. Many patients present with advanced locoregional disease (stage III/IV), which has a poor prognosis, with a 2-year survival rate of <50% [2, 3]. Following treatment of locoregionally advanced disease, the majority of patients will relapse, most (70%–80%) at locoregional sites [4, 5]. At this stage, treatment is generally palliative [6–8]. While a small number of patients with a good performance status (Eastern Cooperative Oncology Group 0–1) may be eligible for salvage surgery and reirradiation [6, 8, 9], most patients will receive chemotherapy, often with a platinum-containing regimen, or best supportive care alone. Median overall survival for these patients is <9 months, and this is only improved to a limited extent by chemotherapy [10, 11].

The treatment of patients with recurrent/metastatic SCCHN is complicated by their generally poor physical condition, often exacerbated by malnourishment and alcohol and tobacco abuse, and comorbidities, such as chronic pulmonary disease [12, 13]. Thus, many patients are not able to withstand an aggressive treatment approach.

Paclitaxel has been shown to be active in induction chemotherapy in locoregionally advanced SCCHN [14]. In recurrent/metastatic SCCHN, paclitaxel administered every 3 weeks as part of first- or subsequent-line therapy appears to be as active as other commonly used regimens [15, 16] but less toxic [17]. Weekly administration of paclitaxel has been shown to be active and well tolerated in breast and lung cancer [18, 19] and has shown antitumor activity in patients with platinum-resistant recurrent/metastatic head and neck cancer [20].

Cetuximab, an epidermal growth factor receptor (EGFR) inhibitor, is active in the treatment of SCCHN [21–23]. It is approved in a number of countries for use in combination with radiotherapy [21] in locally advanced SCCHN, as a single agent in platinum-refractory SCCHN [23] and, more recently, in combination with platinum-based chemotherapy as first-line treatment of recurrent/metastatic disease [22]. In the trial that led to the approval of cetuximab in the first-line treatment of recurrent/metastatic SCCHN [22], there were some adverse events in the cetuximab/platinum/5-fluorouracil (5-FU) arm, including hypomagnesemia and infectious complications, which may have been due to the combination of cetuximab with platinum/5-FU. Evidence indicates that the combination of taxane and platinum-based chemotherapy and cetuximab has greater antitumor activity than cetuximab alone [24, 25], suggesting that this combination may be an effective approach for the treatment of solid tumors.

This phase II study was designed to investigate the efficacy and safety of cetuximab and weekly paclitaxel in the first-line treatment of recurrent/metastatic SCCHN. The influence of cetuximab-associated acne-like rash and tumor EGFR expression or EGFR gene copy number on outcome was also investigated.

Patients and methods

Study design

Patients >18 years of age with histologically confirmed recurrent/metastatic squamous cell carcinoma of the larynx, pharynx and oral cavity and associated organs considered to be unlikely to derive significant benefit from conventional treatment (platinum-based chemotherapy) were enrolled. Other eligibility criteria included: measurable disease (using RECIST), Karnofsky performance status (KPS) ≥70% and adequate hematologic, hepatic and renal functions. Prior systemic chemotherapy was allowed if given as part of a multimodal treatment of locally advanced disease, completed >6 months before study entry. Exclusion criteria included: pregnancy or lactation, prior EGFR inhibitor therapy, prior surgery or radiation therapy within 2 months of study entry and a history of clinically significant cardiac disease or serious neurologic disease. All patients provided written informed consent and the study was approved by the institutional review board of all hospitals involved in the study.

Treatment

Cetuximab was administered by i.v. infusion at an initial dose of 400 mg/m² over 2 h followed by weekly doses of 250 mg/m² over 1 h. Paclitaxel (80 mg/m²) was administered weekly over 1 h, an hour after cetuximab infusion. All patients received prophylactic dexamethasone (10 mg i.v.) and diphenhydramine (50 mg i.v.) before cetuximab, and cimetidine (300 mg i.v.) or ranitidine (50 mg i.v.) before paclitaxel. Treatment was scheduled to continue until disease progression (PD) or unacceptable toxicity.

Dose reductions/delays

In the case of cetuximab-related grade 3 skin toxicity, cetuximab could be delayed for up to two consecutive weeks, followed by dose reductions to...
200 mg/m² and then 150 mg/m² should skin toxicity occur for a second or third time and fail to resolve following dose delay. In the case of grade 3 toxicity persisting for >2 weeks despite dose reduction or delay, or grade 4 toxicity, the patient was to be withdrawn from the trial. Reduced rate cetuximab infusions were allowed in the case of grade 1 and 2 infusion-related reactions (IRRs). Cetuximab was to be discontinued in the case of grade 3 or 4 cetuximab-related IRRs; paclitaxel doses were to be reduced by 25% for neurotoxicity ≥grade 3, other nonhematologic grade 3/4 toxic effects and for grade 4 hematologic toxicity. Paclitaxel dose delays of up to 2 weeks were allowed in the case of reductions in neutrophil or platelet counts, or the presence of mucositis grade ≥2, on the day of treatment. For patients remaining in the trial, when paclitaxel or cetuximab was to be delayed or discontinued due to toxicity concerns, the combination drug was to be administered as a single agent until PD or unacceptable toxicity.

**patient evaluation and statistical analyses**

The primary objective of this trial was to determine the objective tumor response rate to paclitaxel and cetuximab. Secondary objectives were to determine: the duration of response, progression-free survival (PFS), overall survival and safety. Where tumor tissue was available, EGFR expression was evaluated using immunohistochemistry (IHC) and EGFR gene copy number was determined using FISH. Details of the IHC and FISH [26] methodology used are given in the supplemental information (available at Annals of Oncology online). The degree of EGFR staining was assessed quantitatively in each sample by image analysis and the percentage of cells with membrane immunoreactivity calculated. Tumors showing ≥200% membrane immunoreactivity were scored as positive.

FISH was evaluated without previous knowledge of other genetic, clinical or IHC results. Fluorescence signals in each sample were evaluated and scored as previously described [27]. Tumors showing high polysomy and gene amplification were considered to be FISH positive.

Tumor response was assessed every 6 weeks after the start of treatment until PD, using investigator assessment of computed tomography scan or magnetic resonance imaging, according to RECIST criteria [28]. Time to response was defined as the time from the first infusion until complete response (CR) or partial response (PR). Duration of response was defined as the time from the first response (CR or PR) until PD. PFS was defined as the time from the first administration of study treatment until PD or death. Overall survival was defined as the time from the first administration of study treatment to death from any cause. After PD, follow-up visits were conducted every 3 months to determine survival status. Adverse events were recorded at each weekly visit and coded according to the National Cancer Institute—Common Terminology Criteria for Adverse Events, version 3.0.

Continuous variables were summarized using descriptive statistics. Qualitative variables were summarized using counts and percentages. Two-sided confidence intervals (CIs) according to Clopper and Pearson [29] were calculated for response and disease control rates. Kaplan–Meier estimates were used for time-to-event variables [30]. The efficacy analyses were conducted on the intention-to-treat (ITT) population (defined as all patients enrolled on to the study who received at least one dose of the study treatment). Analyses of the relationships between previous chemotherapy and acene-like rash and efficacy and of relationships between tumor EGFR gene copy number and tumor EGFR expression and efficacy were conducted using the Wilcoxon signed rank test for survival and Fisher’s exact test for best overall response. Statistical analyses were carried out using SAS Software, version 8.2 (SAS Institute Inc., Cary, NC). Recruitment of patients into the study was carried out according to a two-stage Simon study design. Eleven patients were included in the first stage in order to exclude a poor response rate (<25%) to treatment. Should all 11 patients fail to respond, the study would be closed. Otherwise, recruitment would continue in a second stage.

**results**

**patients**

Between April and October 2006, 46 patients were enrolled into the study (supplemental Figure S1, available at Annals of Oncology online). All received at least one dose of treatment and were included in the ITT population. Four patients were withdrawn of treatment before the first evaluation visit (week 6) for nontreatment-related issues (cardiac arrest, renal failure, unrelated disease/event, consent withdrawn: n = 1 in each case).

The median age was 59 years (range 42–78 years), 96% of the patients were male and 61% had a KPS of 70%–80% (Table 1). The most common primary tumor sites were the larynx (33%) and pharynx (30%) and the most common disease extent was locoregional recurrence only (48%). Forty-three patients had received previous therapy, 16 of whom had received previous platinum therapy. The three patients who had not received previous treatment had metastatic disease at diagnosis. All patients receiving previous therapy had achieved a CR to the treatment used.

**treatment**

Details of treatment compliance are shown in supplemental Table S1 (available at Annals of Oncology online). Two patients did not receive paclitaxel due to inclusion criteria violations. Altogether, treatment was delayed in 65% of patients receiving cetuximab and in 63% of patients receiving paclitaxel: in ~20% of these patients, treatment delay was due to treatment-related toxicity. Treatment delays (30% with cetuximab and 33% with paclitaxel) were between 4 and 8 days in duration and the most frequent causes of cetuximab or paclitaxel delay were rash, neutropenia and asthenia. Temporary treatment discontinuation due to related adverse events was reported for 12 patients receiving paclitaxel (all with grade 3 neuropathy and paraesthesia) and for 7 patients receiving cetuximab. Before paclitaxel discontinuation, the median number of cycles received by patients was 27 (range 1–47), equivalent to 6 months of treatment, with 10 of the 12 patients receiving >10 cycles of treatment. Two patients withdrew from the study treatment due to treatment-related toxicity (grade 3 conjunctivitis and grade 4 febrile neutropenia). There were no toxic deaths.

**tumor response and survival**

The overall response rate was 54% (95% CI 39% to 69%), with a CR rate of 22% (95% CI 11% to 36%) and a PR rate of 33% (95% CI 20% to 48%) (Table 2). The disease control rate (CR, PR plus stable disease) was 80% (95% CI 66% to 91%). The CR rates for locoregionally recurrent disease alone, metastatic disease alone or both were 15%, 4% and 2%, respectively. Corresponding PR rates were 9%, 11% and 13%. However, there was no difference in the overall response rates between patients with locoregional recurrence and those with metastatic disease. The median time to tumor response was 46 days (range 29–114 days) and the median duration of response was 131.5 days (range 42–490 days).

The median PFS in the ITT population was 4.2 months (95% CI 2.9–5.5 months) (Figure 1A) and the median overall survival was 8.1 months (95% CI 6.6–9.6 months) (Figure 1B). At the time of analysis, the median follow-up was 8.1 months (range 1–144 months) and the median follow-up was 8.1 months (range 1–144 months).
Table 1. Patient and disease characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>44 (96)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>59 (42–78)</td>
</tr>
<tr>
<td>Karnofsky performance status</td>
<td></td>
</tr>
<tr>
<td>90%–100%</td>
<td>18 (39)</td>
</tr>
<tr>
<td>70%–80%</td>
<td>28 (61)</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>15 (33)</td>
</tr>
<tr>
<td>Pharynx</td>
<td>14 (30)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Nonclassifiable</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Transglottic</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Mandible</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pyriform sinus and base of tongue</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (26)</td>
</tr>
<tr>
<td>Lip and oral cavity</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Lips</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Tongue</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Gingival</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Previous treatment (primary tumor)</td>
<td></td>
</tr>
<tr>
<td>Surgery plus radiotherapy</td>
<td>15 (32)</td>
</tr>
<tr>
<td>Surgery plus concomitant chemoradiotherapy</td>
<td>10 (22)</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Induction chemotherapy	 plus concomitant chemoradiotherapy (after ICT)</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Primary concomitant chemoradiotherapy</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Primary radiotherapy</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Previous platinum as part of chemoradiotherapy</td>
<td>16 (94)</td>
</tr>
<tr>
<td>Previous paclitaxel as part of chemoradiotherapy</td>
<td>1 (6)</td>
</tr>
<tr>
<td>No previous treatment</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
</tr>
<tr>
<td>Locoregional recurrence alone</td>
<td>22 (48)</td>
</tr>
<tr>
<td>Metastatic disease alone</td>
<td>13 (28)</td>
</tr>
<tr>
<td>Locoregional recurrence plus metastatic disease</td>
<td>11 (24)</td>
</tr>
</tbody>
</table>

*Including one oropharyngeal tumor.
†Docetaxel/cisplatin/5-fluorouracil (n = 3).
‡As a proportion of patients receiving concomitant chemoradiotherapy.
ICT, induction chemotherapy.

0.8–25.6 months) and 3 of 46 (7%) patients were still alive without evidence of disease.

association between receipt of previous chemotherapy, development of rash, tumor EGFR status and efficacy

Twenty-nine patients had not previously received chemotherapy. Overall, these patients had a significantly better tumor response (P = 0.020) to treatment than those who had received prior chemotherapy (supplemental Table S2, available at Annals of Oncology online) but not a significantly better overall survival (P = 0.529) (supplemental Table S2, available at Annals of Oncology online) or PFS (P = 0.585).

Table 2. Tumor response

<table>
<thead>
<tr>
<th>Best response</th>
<th>Number of patients (n = 46)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>95% CI</td>
<td>11% to 36%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>95% CI</td>
<td>20% to 48%</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>95% CI</td>
<td>14% to 41%</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>95% CI</td>
<td>4% to 23.6%</td>
<td></td>
</tr>
<tr>
<td>Not evaluable</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>25</td>
<td>54</td>
</tr>
<tr>
<td>95% CI</td>
<td>39% to 69%</td>
<td></td>
</tr>
<tr>
<td>Disease control rate (CR + PR + stable disease)</td>
<td>37</td>
<td>80</td>
</tr>
<tr>
<td>95% CI</td>
<td>66% to 91%</td>
<td></td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; CI, confidence interval.

Sixteen patients developed grade 0–1 acne-like rash and 30 developed grade 2–4 rash. There was a significant association between the development and grade of rash and response to treatment (supplemental Table S2, available at Annals of Oncology online). Seven of 10 CRs and 12 of 15 PRs were among patients with grade 2–4 rash. Stable disease was also more common among patients with grade 2–4 rash. However, there was no significant association between rash and overall survival (supplemental Table S2, available at Annals of Oncology online).

Among 29 patients with tumor tissue available for FISH analysis, 25 (86%) had FISH-negative tumors and 4 (14%) had FISH-positive tumors. Tumor FISH status (negative versus positive) did not significantly influence achievement of a response (64% versus 50%, P = 0.622), development of grade 2–4 rash (72% versus 25%, P = 0.105), median PFS (3.8 versus 3.3 months, P = 0.874) and median overall survival (7.3 versus 3.3 months, P = 0.796). Among 33 patients undergoing tumor IHC analysis, 17 (52%) had low EGFR expression and 16 (48%) had high EGFR expression. Tumor EGFR expression (low versus high) did not significantly influence achievement of a response (59% versus 44%, P = 0.494), development of grade 2–4 rash (76% versus 56%, P = 0.282), median PFS (3.3 versus 4.5 months, P = 0.147) and median overall survival (6.5 versus 8.1 months, P = 0.226).

safety and tolerability

Treatment-related grade 3–4 adverse events were reported in 30 patients (65%) (Table 3), the most common of which were acne-like rash (24%), asthenia (17%) and neutropenia (13%), with grade 3/4 febrile neutropenia in 1 patient. Grade 3 IRRs were observed in two patients during paclitaxel infusion. These reactions were managed with medication and treatment delay and both patients then continued in the study until PD. Grade 3/4 gastrointestinal toxicity and renal toxicity were reported in 3% and 5% of patients, respectively. Commonly occurring lower grade treatment-related adverse events included: grade 1–2 conjunctivitis (15%) and peripheral neuropathy (4%); grade 1–3 alopecia (13%), grade 1–2 diarrhea (22%) and...
vomiting (22%) and grade 1–3 onycholysis (24%). Grade 1–2 hypomagnesemia was reported in seven patients (15%). Only two patients withdrew from the study due to treatment-related toxicity (conjunctivitis grade 3 and febrile neutropenia grade 4). No toxic deaths were recorded and in general treatment was well tolerated.

**discussion**

The results of this trial show that the combination of weekly paclitaxel and cetuximab is active in the first-line treatment of recurrent/metastatic SCCHN, with a response rate of 54% and a median overall survival time of 8.1 months. Given that the phase III EXTREME trial provides the gold standard data in this setting by which other trials will be judged, it is interesting to compare our results with those of the EXTREME trial, although one should bear in mind the usual caveats associated with comparing a phase II with a randomized phase III trial. The response rate with the combination of paclitaxel and cetuximab was higher than that achieved with first-line platinum/5-FU with or without cetuximab in the EXTREME trial (36% and 20%, respectively) [22], although the median PFS and overall survival were similar with both regimens. Tumor response is an important consideration in the selection of treatment of patients with recurrent/metastatic SCCHN, with the potential to offer a better quality of life and improve symptom control. In our study, the CR rate was 22% and there appeared to be a higher proportion of CRs among patients with locoregionally recurrent disease only than among those with metastatic disease only (15% versus 4%), although the number

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*Figure 1.* Kaplan–Meier plots for (A) progression-free survival and (B) overall survival. ITT, intention-to-treat.
Diarrhea 1 (2)
IRR, infusion-related reaction.
shown were considered particularly relevant for the agents used.

including survival, response rate and a range of biological markers,
addition, the EXTREME study found no relationship between
cetuximab for recurrent/metastatic SCCHN [22, 32, 33]. In
SCCHN [31], such a relationship is less clear in trials of
cetuximab and radiotherapy in patients with locally advanced
between rash and outcome has been demonstrated for
identified in patients with SCCHN. While a relationship
was 16.0 and 14.0, respectively.
PFS or overall survival. Compliance with treatment was good
chemotherapy as might be expected. However, the receipt of

treatment of locally advanced disease. It is worth noting that
of the fact that this was a patient population with a poor

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Table 3. Acute grade 3 to 4 toxic effects occurring with an incidence of

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>30 (65)</td>
</tr>
<tr>
<td>Acne-like rash</td>
<td>11 (24)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Neuropathy/paresthesias</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>2 (4)</td>
</tr>
<tr>
<td>IRRs*</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

*IRRs: both were considered to be due to paclitaxel. The adverse events shown were considered particularly relevant for the agents used.
IRR, infusion-related reaction.

of patients included in the analysis is too small to allow firm
conclusions to be drawn. The median duration of response of
131.5 days (4.3 months) was also similar to that obtained with
platinum/5-FU alone in the EXTREME trial.

In our trial, the median PFS (4.2 months) and the median
overall survival (8.1 months) were similar than those seen with
platinum/5-FU alone in the EXTREME study (3.3 and 7.4
months, respectively) and only slightly lower than those
obtained with cetuximab/platinum/5-FU in first-line studies
(5.6 and 10.1 months, respectively [22]).

The results of our study are particularly encouraging in view
of the fact that this was a patient population with a poor
prognosis: a high proportion of patients (61%) had a KPS of
70%–80% and 33% had received platinum-containing
treatment of locally advanced disease. It is worth noting that
tumor response was poorer among patients receiving previous
chemotherapy than in those not receiving previous
chemotherapy as might be expected. However, the receipt of
previous chemotherapy was not significantly associated with
PFS or overall survival. Compliance with treatment was good
and the median numbers of cetuximab and paclitaxel infusions
were 16.0 and 14.0, respectively.

To date, no surrogate marker of cetuximab activity has been
identified in patients with SCCHN. While a relationship
between rash and outcome has been demonstrated for
cetuximab and radiotherapy in patients with locally advanced
SCCHN [31], such a relationship is less clear in trials of
cetuximab for recurrent/metastatic SCCHN [22, 32, 33]. In
addition, the EXTREME study found no relationship between
survival, response rate and a range of biological markers,
including EGFR gene copy number [26]. In our study, there
was some association between rash and response but not
between rash and overall survival. No significant association
between tumor EGFR status or tumor EGFR gene copy
number and the development of grade 2–4 rash and efficacy
was identified. The numbers of patients involved in our
analyses were low and should not provide the basis for
speculation.

In general, the tolerability of this regimen was acceptable. It
is of note that the group of 12 patients who discontinued
chemotherapy due to adverse events did so after being able to
receive a median of 6 months of treatment. The adverse
events observed in our study were those expected with the
agents used. Grade 3/4 IRRs were reported in only two
patients. Asthenia is commonly observed with paclitaxel and
platinum. Grade 3/4 asthenia was reported in 17% of patients
in this study. In the EXTREME trial, the proportion of
patients receiving platinum/5-FU/cetuximab who developed
grade 3/4 asthenia was much lower than in our trial (5%) and
not significantly different from that seen with platinum/5-FU
(6%) [22]. The discrepancy may be due to differences in the
stage of the underlying disease of the patients in the studies.
In contrast to what is seen with platinum chemotherapy, the
incidence of grade 3/4 gastrointestinal and renal toxic effects
was low (3% and 5%, respectively). In our study, onycholysis
was observed in 24% of patients at a highest grade of 3.
Although nail disorders are a known side-effect of cetuximab,
onycholysis has not been reported in other head and neck
trials with cetuximab [22, 32, 34], and it may be that this
toxicity results from an interaction between paclitaxel and
cetuximab.

The current first-line standard treatment approach for
recurrent/metastatic SCCHN is the combination of platinum/
5-FU and cetuximab [22]. However, the activity and
tolerability of the weekly paclitaxel/cetuximab combination
suggest that it may be a suitable first-line treatment option
for patients in a poor state of health, particularly where
platinum-based chemotherapy is contraindicated. It may also
be an effective option for patients with recurrent/metastatic
SCCHN who have failed first-line platinum-containing
chemotherapy, and for whom there are few treatment options
[11], this is currently being investigated in a phase II trial
being conducted by the Spanish Head and Neck Cancer
Cooperative Group.

In conclusion, our trial demonstrates that cetuximab plus
weekly paclitaxel is active as first-line treatment of recurrent/
metastatic SCCHN. While platinum/5-FU/cetuximab remains
the standard first-line treatment approach, cetuximab plus
weekly paclitaxel may be an appropriate choice for poor
performance status patients.

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references