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Feasibility of 6-month maintenance cetuximab after adjuvant concurrent chemoradiation plus cetuximab in squamous cell carcinoma of the head and neck

The management of squamous cell cancer of the head and neck (SCCHN) has become increasingly complex, because combined interdisciplinary treatment approaches including new diagnostic procedures are used on a routine basis [2, 9, 12, 14, 21, 23]. Treatment varies depending on tumor location, spread, and patient-associated factors, including age and performance status. For unresected disease, the combination of concurrent chemoradiation has been shown to be more effective than sole radiotherapy (RT) in several randomized trials and is, therefore, considered standard of care in this situation. Although the role of surgery in locally advanced disease is not well defined, many centers prefer surgery of the primary tumor in combination with therapeutic and elective neck dissections, if the expected functional outcome is deemed acceptable for the patient from the surgical perspective. In a number of nonrandomized com-

parisons, adjuvant radiotherapy resulted in a substantial benefit, thus, deeming a randomized comparison inappropriate. As in unresectable SCCHN, concurrent chemoradiation was also shown to be more effective than sole radiotherapy in three large independent randomized trials in the postoperative setting [5, 10, 15]. A meta-analysis of two of these trials (RTOG 9501, [11] and EORTC 22931, [5]) indicated that concurrent chemoradiation is especially beneficial in terms of locoregional tumor control and overall survival, if at least one of the following high risk features is present: lymph node involvement with extracapsular tumor extension (ECE) or close surgical resection margin <5 mm [5]. Concurrent chemoradiation is, therefore, considered standard of care for patients with these high risk features. Adjuvant radiotherapy was administered in conventional fractionation (5 fractions of 2 Gy per week) to total doses of

64 [13] up to 66 Gy [5, 10]. Concurrent chemotherapy consisted either of cisplatin 20 mg/m² and continuous infusion of 5-FU 600 mg/m² on days 1–5 and 29–33, or of cisplatin 100 mg/m² on days 1, 22, and 43 [5, 10]. The prognosis of patients with high risk of recurrence remained unsatisfactory in spite of concurrent chemoradiation. The 5-year overall survival with concurrent adjuvant chemoradiation was no better than approximately 50%. According to the patterns of failure analysis locoregional and distant recurrences occurred with the same frequency. This indicates that more effective approaches, attacking locoregional disease and distant metastases, are needed.

In SCCHN, high levels of epidermal growth factor receptor 1 (EGFR1) are almost always expressed. Since EGFR1 mutations and K-RAS mutations are rare in HNSCC, the prerequisites for an effective treatment with blocking anti-EGFR1 an-

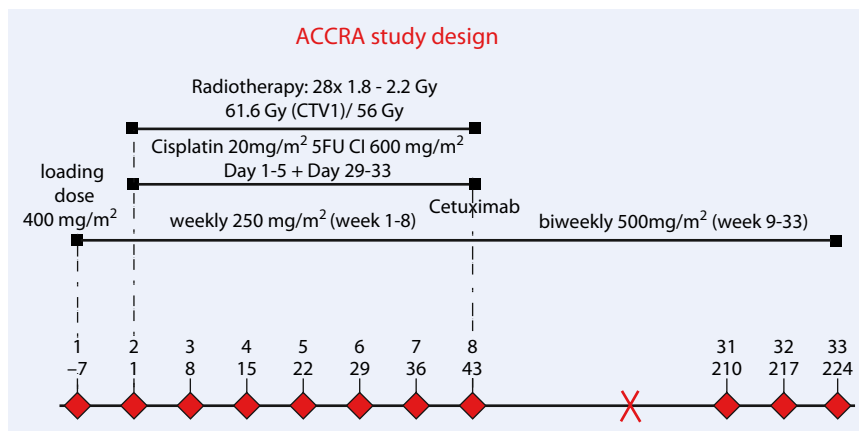


Fig. 1 ▲ Study design

tibodies, like cetuximab, are met. Animal studies on human SCCHN presumed additive and synergistic effects for the combination of cetuximab with both radiotherapy and cisplatin [20, 22].

Consequently, concomitant administration of cetuximab during 6–7 weeks of RT was tested in unresected locally advanced SCCHN, demonstrating improved locoregional tumor control and overall survival [7]. This phase III trial led to a marketing authorization approval both in Europe and the USA. The most relevant toxicities of radiotherapy in SCCHN, like mucositis and swallowing problems, were not reported to be significantly increased by the addition of cetuximab. As the main additional toxicity induced by cetuximab, the rate of grade III–IV acute skin reactions was increased as expected. The magnitude of the observed benefit was in the same range as for adding cisplatin-based chemotherapy concurrently to radiotherapy. A direct comparison of chemoradiation to concurrent cetuximab and radiotherapy has not been published. Cetuximab given for 6 weeks concurrently to radiotherapy did not result in a significant reduction of the distant metastases rate.

Based on these considerations, we evaluated the feasibility and efficacy of adjuvant chemoradiation with concomitant and maintenance cetuximab therapy in patients with high risk of locoregional and distant recurrence in a phase II trial. Here, we present the interim results of the open label multicenter phase II trial focusing on feasibility and acute toxicity of the regimen.

Patient and methods

A multicenter, uncontrolled open-label phase II trial was performed to evaluate safety and efficacy of post-operative radiochemotherapy (RCT) in combination with cetuximab in SCCHN patients. The primary objective was the rate of patients experiencing grade 3 or 4 acute toxicities on skin and mucosa. The secondary objectives of this study were the 2-year disease-free survival rate, the incidence of locoregional relapses, progression-free survival, overall survival, the rate of patients with secondary primary neoplasm, and the incidence of late toxicity.

The study was conducted at 10 investigational sites recruiting in Germany from May 2008 until December 2010. Eligible patients had a diagnosis of histologically confirmed, surgically resected squamous cell carcinoma (SCC) of the oropharynx, larynx, or oral cavity with high risk of locoregional recurrence, receiving cetuximab in combination with cisplatin and 5-FU (■ Fig. 1).

Inclusion in the study required signed written informed consent, age between 18 and 70 years and the following:

- Surgically resected SCC of the hypopharynx, oropharynx, larynx, and oral cavity with high risk of locoregional recurrence not more than 9 weeks prior to treatment. To be categorized as high risk, the patient has to fulfill at least one of the following criteria:
 - R0 resection <5 mm margin,
 - R1 resection or
 - Extracapsular nodal extension.
- No previous chemotherapy/RT.

- Performance status ECOG 0–1.
- Additionally patients required contraception if of childbearing age.
- Adequate renal, liver, and hematological functions (within maximum 9 weeks until surgery):
 - Adequate bone marrow function (neutrophils $>1.5 \times 10^9/l$, platelets $>100 \times 10^9/l$, hemoglobin >10.0 g/dl),
 - Adequate liver function (bilirubin <2.0 mg/dl, AST, ALT, AP, γ -GT $<3 \times$ ULN),
 - Adequate renal function (creatinine clearance ≥ 60 ml/min).
- No distant metastases.

Excluded were patients with nasopharyngeal carcinoma, R2 resection, invalid informed consent or other serious illness or medical conditions.

Patients received an initial dose of cetuximab, 400 mg/m² intravenously (i.v.) over 120 min 4–10 days prior to the start of RCT. No chemotherapy or RT was given during this time period. The treatment started not later than postoperative day 56 in an effort to commence radiation by postoperative day 63.

The *clinical target volume 1* (CTV1) included the operative bed of the primary tumor and the area of the lymph nodes with extracapsular spread typically with a 1 cm margin with a minimum of 5 mm except in those areas where the former tumor bed was immediately adjacent to structures known to be uninvolved.

The *clinical target volume 2* (CTV2) included the lymph nodes areas with subclinical metastases but without extracapsular spread (dissected neck area containing lymph node metastases) typically with a 1 cm margin with a minimum of 5 mm except in those areas where the involved nodes were immediately adjacent to structures known to be uninvolved.

The *clinical target volume 3* (CTV3) included the lymph node groups or surgical neck levels without metastases typically with a 5 mm margin except in those areas where the lymph nodes were immediately adjacent to structures known to be uninvolved.

The following lymph node groups at risk were included into the CTV3:

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Feasibility of 6-month maintenance cetuximab after adjuvant concurrent chemoradiation plus cetuximab in squamous cell carcinoma of the head and neck**Abstract**

Background. Close resection margins <5 mm (CM) or extra capsular extent at the lymph nodes (ECE) impair the prognosis of patients with squamous cell cancer of the head and neck (SCCHN) scheduled for adjuvant radiochemotherapy. We conducted a multicenter phase II study to investigate toxicity and efficacy of additional cetuximab administered concomitantly and as maintenance for the duration of 6 months following adjuvant radiochemotherapy. Preliminary results on feasibility and acute toxicity on skin and mucosa are presented in this article.

Methods. Patients with SCCHN following CM resection or with ECE were eligible for the study. In all, 61.6 Gy (1.8/2.0/2.2 Gy, days 1–36) were administered using an integrated boost intensity-modulated radiotherapy (IMRT) technique. Cisplatin (20 mg/m²,

days 1–5 and days 29–33) and 5-fluorouracil (5-FU) as continuous infusion (600 mg/m², days 1–5 + days 29–33) were given concurrently. Cetuximab was started 7 days prior to radiochemotherapy at 400 mg/m² followed by weekly doses of 250 mg/m². Maintenance cetuximab began after radiochemotherapy at 500 mg/m² every 2 weeks for 6 months.

Results. Of the 55 patients (46 male, 9 female, mean age 55.6, range 29–70 years) who finished radiochemotherapy, 50 were evaluable for acute toxicity concerning grade III/IV toxicities of skin and mucosa. Grade 3–4 (CTC 3.0) mucositis, radiation dermatitis, and skin reactions outside the radiation portals were documented for 46, 28, and 14% of patients, respectively. One toxic death occurred (peritonitis at day 57). Cetuximab was terminated in 5 patients due to al-

lergic reactions after the first application. In addition, 22% of patients discontinued cetuximab within the last 2 weeks or at the end of radiochemotherapy. Of patients embarking on maintenance treatment, 80% were still on cetuximab at 3 months and 63% at 5 months. Concurrent and maintenance treatment with cetuximab could be administered as scheduled in 48% of patients.

Conclusion. Adjuvant radiochemotherapy with concomitant and maintenance cetuximab is feasible and acute toxicities are within the expected range. Compliance within the first 3–5 months is moderate.

Keywords

Adverse effects · Clinical trial, phase II · Head and neck neoplasms · Toxicity · Interim analysis

Durchführbarkeit einer 6-monatigen Cetuximab-Erhaltungstherapie nach adjuvanter gleichzeitiger Chemoradiotherapie plus Cetuximab bei Plattenepithelkarzinomen des Kopf-Hals-Bereichs**Zusammenfassung**

Hintergrund. Die Prognose von Patienten mit Plattenepithelkarzinomen im Kopf-Hals-Bereich (SCCHN, „squamous cell cancer of the head and neck“) nach adjuvanter Radiochemotherapie ist weiterhin unbefriedigend, sofern <5 mm im Gesunden reseziert wurde oder an den Lymphknoten ein extrakapsuläres Wachstum (ECE) nachweisbar war. Aus diesem Grund führten wir eine multizentrische Phase-II-Studie zur Untersuchung der Toxizitäten und der Wirksamkeit der adjuvanten Radiotherapie in Kombination mit Cisplatin, 5-Fluorouracil (5-FU) und Cetuximab gefolgt von einer Erhaltungstherapie mit Cetuximab für 6 Monate durch. In dieser Publikation präsentieren wir eine Interimsanalyse zur Durchführbarkeit und Akuttoxizität an Haut und Schleimhäuten.

Methodik. Patienten, mit Plattenepithelkarzinomen im Kopf-Hals-Bereich, die operiert wurden und bei denen ein hohes Risiko für ein Lokalrezidiv bestand (Resektionsrand <5 mm; ECE), wurden in die Studie eingeschlossen. Die Strahlentherapie erfolgte mit integrierter Boost-IMRT-Technik (1,8/2,0/2,2 Gy, Tage 1–36) bis zu einer Gesamtdosis von 61,6 Gy. Als Chemotherapie

wurden Cisplatin (20 mg/m² Tag 1–5 und Tag 29–33) und 5-Fluorouracil (5-FU) als kontinuierliche Infusion (600 mg/m² Tag 1–5 plus Tag 29–33) simultan zur adjuvanten Radiochemotherapie gegeben. Die Gabe von Cetuximab begann 7 Tage vor Start der Radiochemotherapie mit einer Dosierung von 400 mg/m² durch wöchentliche Cetuximab-Gaben (250 mg/m²) während der kombinierten Radiochemotherapie. Die Cetuximab-Erhaltungstherapie betrug nach Abschluss der Radiochemotherapie 500 mg/m² alle 2 Wochen über einen Zeitraum von 6 Monaten.

Ergebnisse. Von 55 Patienten (46 Männer, 9 Frauen, Durchschnittsalter 55,6 Jahre, Spanne 29–70 Jahre), die die kombinierte Therapie (Radiochemotherapie + Cetuximab) beendeten, konnten bei 50 Patienten die Akuttoxizitäten Grad 3–4 an Haut und Schleimhaut anhand der CTC-3.0-Kriterien ausgewertet werden. Simultan zur kombinierten Radiochemotherapie war bei 46% der Patienten eine Mukositis vom Grad 3–4, bei 28% der Patienten eine Hautreaktion vom Grad 3–4 im Bestrahlungsfeld und bei 14% der Patienten eine Hautreaktion außerhalb des Bestrahlungsfeldes vom Grad 3–4

zu verzeichnen. Ein Patient verstarb an einer Peritonitis am Tag 57. Bei 10% der Patienten wurde die Cetuximab-Gabe nach der ersten Anwendung (allergische Reaktionen) beendet. Die Cetuximab-Therapie wurde von 22% aller Patienten vor Abschluss der Radiochemotherapie beendet. Von allen Patienten, die mit der Cetuximab-Erhaltungstherapie begonnen haben, erhielten 80% Cetuximab noch nach 3 Monaten, 63% noch nach 5 Monaten und 48% beendeten die komplette Cetuximab-Erhaltungstherapie nach 6 Monaten.

Schlussfolgerung. Die adjuvante Radiochemotherapie mit Cetuximab gefolgt von einer Cetuximab-Erhaltungstherapie ist durchführbar und nicht mit unerwartet hohen Nebenwirkungen verbunden. Die Compliance bei der Erhaltungstherapie mit Cetuximab ist innerhalb der ersten 3–5 Monate befriedigend.

Schlüsselwörter

Unerwünschte Nebenwirkungen · Klinische Phase-II-Studie · Kopf-Hals-Neoplasien · Toxizität · Interimanalyse

Tab. 1 Clinical outcome for patients with high risk head and neck cancer

	5-year locoregional failure (%)	5-year distant metastasis (%)
EORTC #22931	18	21
RTOG #9501	19	20
ARO	11	25

EORTC European Organization for Research and Treatment of Cancer, RTOG Radiation Therapy Oncology Group, ARO "Arbeitsgemeinschaft Radiologische Onkologie" (Association for Radiation Oncology).

Tab. 2 Patient characteristics

	n	T1–T2	T3	T4	N0	N1	N2 (incl. a/b/c)	N3
Oro-/Hypo-pharynx	35	27	5	3	2	5	25	3
Larynx	4	3	1	0	2	0	2	0
Oral cavity	16	9	4	3	2	6	8	0
Total	55							

Tab. 3 Surgical characteristics of patients

	Yes	No	Unknown
R0 resection <5 mm margin	23	29	3
R1 resection	19	34	2
Extracapsular nodal extension	34	20	1

Tab. 4 Patient compliance

Radiotherapy (n=55)	95–105% of prescribed dose (61.6 Gy) n=49 5 patients: data pending, 1 patient interrupted radiotherapy at 55 Gy for unknown reason
Chemotherapy (n=55)	100%, n=37 90%, n=3 Patient 1: cisplatin: 100%, 5-FU: 60% (bradycardia) Patient 2: cisplatin: 80%, 5-FU: 80%. Patient 3: cisplatin: 90%, 5-FU: 90% (interruption due to port implantation) 75%, n=1 Cisplatin: 100%, 5-FU: 75% (mucositis ^{III}) 65%, n=1 Cisplatin: 50% (no 2nd cycle, adverse event: polyneuropathia grade III) 5-FU: 80% (problems with central line) 50%, n=5 1. Cisplatin: 50%, 5-FU: 50% (no 2nd cycle) 2. Cisplatin: 50%, 5-FU: 50% (no 2nd cycle) 3. Cisplatin: 50%, 5-FU: 50% (no 1st cycle) 25%, n=1 Cisplatin: 25%, 5-FU: 0% 7 patients data pending

- Submental nodes (surgical level IA): in cases where the floor of mouth or level IB were involved.
- Submandibular nodes (surgical level IB): all cases except primary palate tumors which did not extend to the tonsil or base of tongue. Only the ip-

silateral level IB was a target, unless the tumor crossed the midline. Level IB was a target in the neck side with upper jugular metastases in all cases.

- Upper deep jugular (junctional, parapharyngeal) nodes: all cases (at the

neck side ipsilateral to the primary tumor).

- Subdiaphragic (jugulodigastric) nodes, midjugular, lower neck, and supraclavicular nodes (levels II–IV): all cases, bilaterally, except for tonsillar fossa tumors >1 cm from the midline and surgical node negative contralateral neck.
- Posterior cervical nodes (level V): all cases, at the neck side where there is an evidence of jugular nodal metastases.
- Retropharyngeal nodes: all cases.

Prescription dose to the PTVs (planning target volumes) was performed as follows:

- PTV1 received 28 fractions of 2.2 Gy/each, total 61.6 Gy.
- PTV2 received 28 fractions of 2.0 Gy/each, total 56 Gy.
- PTV3 received 28 fractions of 1.8 Gy/each, total 50.4 Gy.

Radiotherapy was delivered once daily, 5 fractions per week, over 5.5 weeks. All targets were treated simultaneously using an integrated boost IMRT technique.

The following guidelines for dose prescriptions to target volumes and organs at risk were provided in the protocol:

- No more than 20% of any PTV received >110% of its prescribed dose.
- No more than 3% of any PTV received <90% of its prescribed dose (exception: skin with a 2–3 mm internal margin, if regarded as region of low risk for recurrence).
- No more than 1% or 1 ml of the tissue outside the PTVs received >110% of the dose prescribed to the primary PTV.

Dose–volume histograms (DVHs) were generated for all critical normal structures and the unspecified tissues. Dose constraints to normal tissues were as follows:

- Planning organ at risk volume (PRV) of the brainstem 54 Gy/ <1/3 of cross sections and <2 ml: 60 Gy,
- PRV of the spinal cord 45 Gy/ <1/3 of cross sections and <2 ml: 54 Gy,
- PRV of the optic nerve 54 Gy,
- PRV of the optic chiasm 54 Gy,
- PRV of the inner ear 54 Gy,
- PRV of the mandible 70 Gy,

- Unspecified tissue outside the targets: <110% of the prescribed dose to PTV 61.6.

Recommended planning goals of the parotid glands were (1) mean dose to either parotid <26 Gy, or (2) at least 50% of the either parotid gland will receive <30 Gy, or (3) at least 20 ml of the combined volume of both parotid glands will receive <20 Gy. For the submandibular/sublingual glands and oral cavity, the dose was reduced as much as possible.

Evaluation of acute toxicity. Acute radiation effects were considered through day 90 of treatment. The NCI Common Toxicity Criteria for Adverse Events (CTCAE) v 3.0 were used to score the toxicities. Reversible radiation dermatitis and mucositis were documented once a week. Other common radiation toxicities included fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, hypogeusia, dysgeusia, dysphagia, and skin erythema and desquamation within the treatment fields, and also recorded was whether a feeding tube was placed for nutritional supplementation. Less common long-term radiation toxicities included hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, cervical fibrosis, and mandibular osteoradionecrosis. These data, especially late effects will be published later.

The interim analysis provided in this publication on the first 55 of 80 planned patients treated in the protocol was restricted to feasibility and acute grade III/IV side effects. The study protocol was approved by the central ethics committee and the institutional review boards of all participating institutions, and each patient provided written informed consent before participating in the study

Statistical analysis

Primary endpoints for this planned interim analysis were toxicity and compliance. All data were collected in an Excel TM (Microsoft Corporation, Redmond, WA, USA) datasheet and transferred to the coordination center for clinical trials at the University of Düsseldorf. Here

the data were stored in a locked database. After carefully checking for faulty entries and extreme values, the data were transferred into Statistica (StatSoft (Europe) GmbH, Hamburg, Germany) for statistical analysis.

Compliance to cetuximab treatment was analyzed using Kaplan–Meier methods, since not all patients had sufficient follow up for planned completion of maintenance therapy.

Results

At the time of analysis 55 of the initially 80 planned patients (46 male, 9 female, mean age 56.6 years, range 29–70 years) completed chemoradiation (patient characteristics are shown in ■ **Tab. 2** and ■ **Tab. 3**). In all, 50 patients were eligible for toxicity analysis. Concurrent CRT plus cetuximab was associated with grade 3–4 (CTC 3.0) mucositis, radiation dermatitis, and skin reaction outside the radiation portals in 46, 28, and 14% of patients, respectively. One event-related mortality occurred (peritonitis at day 57). Due to allergic reactions cetuximab was terminated in 10% (5 patients) of the patients after the first application. In 22% (11 patients) of all patients, cetuximab was discontinued during the last 2 weeks or at the end of CRT. Of those patients receiving maintenance therapy, 80% (40 patients) were still treated with cetuximab after 3 months, 64% (32 patients) after 5 months. 48% (24 patients) completed 6 months maintenance therapy. A total of 25 patients were dependent on nasogastric or PEG feeding tubes. Compliance to 5-FU and cisplatin as well as the compliance to RT was not significantly affected by the cetuximab application.

Concerning chemotherapy and radiotherapy, compliance was good (■ **Tab. 4**).

■ **Fig. 2** shows the Kaplan–Meier plot for the reasons of cessation of cetuximab during the planned treatment. Acute toxicity, especially skin and mucosal toxicity as well as incompliance of the patients were the main reasons for cessation of further cetuximab treatment.

Discussion

The disease-free survival of patients with SCCHN 5 years after surgery and adjuvant chemoradiation is not higher than 36%, if high risk features like extracapsular tumor extension at involved lymph nodes or a close resection margin (<5 mm) is present. The reported benefits for the addition of concurrent cetuximab to radiotherapy in unresected locally advanced SCCHN and for addition of concurrent and maintenance cetuximab to cisplatin and 5-FU in recurrent and metastatic SCCHN prompted us to initiate a phase II trial on adjuvant chemoradiation in combination with concurrent and maintenance cetuximab therapy.

The preliminary results presented here indicate that the regimen is feasible with a grade III/IV acute toxicity within the upper limits of the expected range. As anticipated rates of grade III/IV skin toxicities inside (28%) and outside (14%) the radiation portals were higher than typically reported for adjuvant chemoradiation without cetuximab [1, 10, 13]. The rate of acute grade III/IV mucositis (46%) was in the upper range compared to the experiences of other groups applying adjuvant chemoradiation alone [13, 16]. These observations agree well with the first reports from the RTOG 0522 trial [3] and the CONCERT-1 trial [18]. Within the RTOG 0522 trial, concurrent radiotherapy and cisplatin was tested against the same regimen plus concurrent cetuximab in unresected locally advanced SCCHN. The CONCERT-1 trial tested the same concept, but used panitumumab, a fully humanized anti-EGFR-antibody binding to the identical epitope of the EGFR as cetuximab. In both trials, significantly higher rates of grade III/IV mucosal and skin toxicities were observed. In spite of these higher acute toxicities, the triple therapy did not result in any benefit in locoregional control, progression-free survival, or overall survival. The number of evaluable patients in these trials (RTOG 0522: n=895; CONCERT-1: n=150) appear to be sufficient to exclude a relevant benefit for patients with unresected locally advanced SCCHN from the concurrent addition of an EGFR antibody to chemoradiation. In view of this data, it appears to be very un-

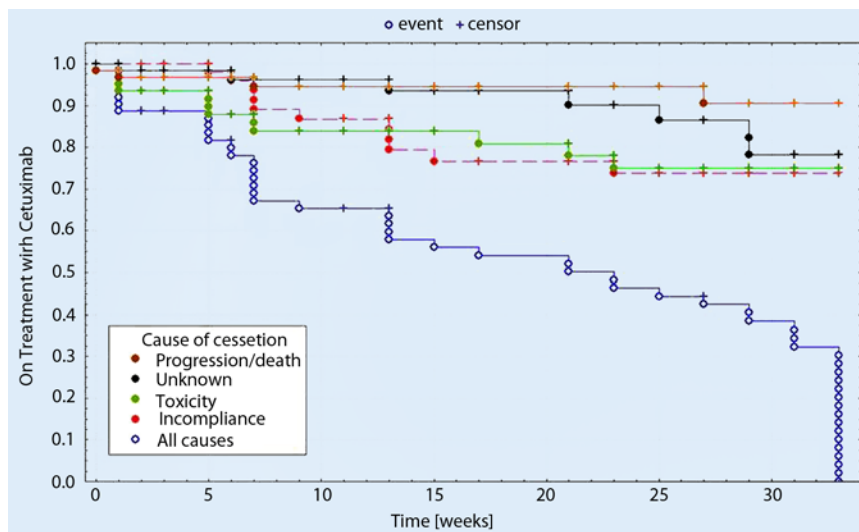


Fig. 2 ▲ Kaplan–Meier estimates the reason of cessation during the study

likely that the addition of cetuximab or panitumumab to adjuvant chemoradiation after surgery will result in a clinical benefit for these patients. Regardless the final oncological outcome of the phase II trial presented here, the further development of the concept of concurrent cetuximab and chemoradiation seems to be a dead end.

The question arises whether maintenance therapy in the clinical setting would do the same. The addition of 6 weeks cetuximab to concurrent chemoradiation in the RTOG 0522 trial resulted in a borderline significant reduction of distant metastases (12.0 vs. 7.6% at 2 years, $p=0.07$). A significantly improved survival was reported in recurrent and metastatic SCCN for adding concurrent and maintenance cetuximab to cisplatin plus 5-FU [24], whereas no significant survival benefit was observed in the same setting for adding concurrent panitumumab without maintenance therapy to cisplatin plus 5-FU (SEPCTRM-1). These observations indicate that there is sound rationale to test maintenance therapy with cetuximab after chemoradiation in SCCN. The data presented here are helpful to judge the potential feasibility of such an approach.

Only two thirds of the included patients started maintenance cetuximab as planned. Reasons for this observation were the comparatively high rate of allergic reactions (10%) after the first application of cetuximab [6, 19] and the rela-

tively high acute mucosa and skin toxicity that caused investigators or patients to discontinue further treatment with cetuximab (■ Fig. 1). Incompliance occurred most frequently directly after completion of chemoradiation in patients, who had experienced a grade III/IV mucosal or skin toxicity at that time. Since chemoradiation without concurrent cetuximab induces less acute toxicity [8, 17], one would expect that a higher percentage of patients would be able and willing to start maintenance cetuximab after chemoradiation alone. Once maintenance therapy with cetuximab had been started, adherence to the protocol was quite satisfactory for the first 3 months (80%), but declined to 63% at 5 months and to 48% at the planned completion of the therapy at 6 months. Only in a few patients was toxicity the reason for cessation of maintenance treatment. Most discontinuations were caused by patient's incompliance and some unknown reasons, the latter most likely also as a result of a patient's incompliance.

The experience with maintenance cetuximab after chemoradiation is otherwise very limited. Argiris et al. [4] tested in a small phase II trial the addition of cetuximab during induction chemotherapy and during concurrent radiotherapy with cisplatin followed by 6 months maintenance therapy with cetuximab in 39 patients with locally advanced SCCN. Neutropenic fever (10%) was the most relevant severe toxicity during the induction phase of the protocol, whereas dur-

ing chemoradiation and concurrent cetuximab grade III/IV mucositis (54%) was the crucial acute toxic reaction. Maintenance cetuximab was started in 31 out of 39 patients (79%). At 5 months, 15 of these 31 patients (48%) were still on treatment. The causes of discontinuation of maintenance treatment with cetuximab were not given in that publication. However, the results regarding the feasibility of maintenance therapy with cetuximab in SCCN are strikingly similar to our experience.

Conclusion

Adjuvant CRT in combination with cetuximab followed by maintenance cetuximab is feasible with an acute mucosal and dermal toxicity at the upper limit of the expected range. Toxicity during 6 months maintenance therapy with cetuximab in SCCN is limited. Compliance to maintenance treatment was satisfactory during the first 3–5 months.

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