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Original Research Article

Phase II study of induction chemotherapy with docetaxel, cisplatin, 5-fluorouracil followed by radioimmunotherapy with cetuximab and intensity-modulated radiotherapy in combination with a carbon ion boost for locally advanced tumors of the oro-, hypopharynx and larynx

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ABSTRACT

Purpose: This phase II trial was designed to evaluate efficacy and safety of a highly intensified therapy in locally advanced squamous cell carcinoma of the oro-, hypopharynx and larynx.
Methods: In this prospective, mono-centric, open-label, non-randomized phase II trial the single treatment arm consisted of a combined induction chemotherapy with docetaxel, cisplatin, 5-fluorouracil, followed by bioradiation with the monoclonal antibody cetuximab, carbon ion boost (24Gy(RBE) in 8 fractions) and IMRT (50 Gy in 25 fractions). The trial was closed early due to slow accrual.
Results: Eight patients (median age 52.5 years) were enrolled into the trial. The median follow-up was 13 months and the 12-months locoregional tumor control, progression-free survival and overall survival rates were 100.0% each. Complete remission was achieved in 7 patients. The most commonly late radiation adverse event was xerostomia (85.7% at 12 months). Five serious adverse events with recovery were documented in 4 patients: mucositis grade 3 (n = 2), decreased lymphocyte count grade 4, febrile neutropenia grade 4 and hypersensitivity grade 3 to cetuximab (n = 1 each). Most symptom scales had their worst value at the last treatment day and recovered until the 4th follow-up visit.
Conclusion: The study treatment was tolerable and promising. Reduced quality of life recovered for most aspects until the last follow-up visit.

1. Introduction

More than 18,000 people are newly diagnosed every year with head and neck cancer in Germany [1]. More than 90% of these malignancies are classified as squamous cell carcinoma of head and neck (SCCHN). For small localized SCCHN of lower stages (stages I and II) surgery and/or radiation are the therapies of choice and generally show favourable outcomes. For patients with locally or regionally advanced disease (stages III and IV) the prognosis is much worse. Platinum-based chemoradiation achieved locoregional control rates of >75% at 5 years in advanced laryngeal carcinoma [2] but only up to approximately 58% in other head and neck sites [3]. This translates into overall survival rates of less than 50% at 5 years [3,4]. Clearly, this outcome is less than satisfactory but further intensification of treatment unfortunately also increases toxicity burden which reaches patient tolerable limits [5].

The use of induction chemotherapy followed by radiotherapy or chemoradiation is a treatment option for laryngeal SCCHN which could show good 5-year overall and progression-free survival rates in two independent trials [6,7]. Docetaxel, cisplatin, 5-fluorouracil (TPF) induction therapy significantly improved survival without substantial increase in grade 3/4 toxicity as compared to PF induction [6,7].

Other promising approaches include targeted therapy with monoclonal antibodies. Since the expression of epidermal growth factor receptor (EGFR) is present in nearly 90% of SCCHN cases [8], EGFR is a potential target for therapy. This receptor and its

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ligands play a crucial role in proliferation, differentiation, anti-apoptotic signaling, processes of angiogenesis and metastasis [9]. Furthermore, high expression of EGFR is associated with increased tumor size, decreased radiation sensitivity and increased risk of recurrence in SCCHN [10,11]. Results of a phase 2 study suggest that radioimmunotherapy with cetuximab might be used as an alternative to chemoradiotherapy with cisplatin to reduce toxicity of the treatment [12], however; recently the results on the GORTEC 2007-002 trial were published showing that induction chemotherapy followed by radioimmunotherapy is not superior to chemoradiotherapy and might have more treatment related toxicity [13].

More over the development of highly sophisticated radiation techniques such as IMRT was shown to reduce late sequelae (i.e. higher-grade xerostomia) while achieving more conformal dose distributions with sparing of critical organs at risk [14]. Carbon ion therapy has shown to have very beneficial effects in comparatively radio-resistant tumors such as malignant salivary gland tumors, chordoma, and chondrosarcoma [15,16]. In addition, the tumoricidal effect of high linear energy transfer (LET) radiation is independent of the oxygen effect and hence attractive especially in tumors with necrotic areas and hypoperfusion such as advanced SCCHN. Especially the administration of carbon ions allows the highly localized deposition of energy that can be utilized for increasing radiation doses to tumors while minimizing dose to surrounding tissue. Furthermore, carbon ions might have beneficial effects on tumor stem cells' migration and invasion [17].

TPF-C-HIT was a phase II trial designed to evaluate efficacy and safety of a highly intensified therapy combining very effective treatment approaches in head and neck oncology. Patients received induction chemotherapy with TPF followed by combined bioradiation with weekly cetuximab and IMRT plus carbon ion boost.

2. Methods

In this study a combination of three methods was conducted. As an investigational multimodal therapy the following treatment was applied: induction chemotherapy with TPF, monoclonal antibody therapy with cetuximab and radiotherapy (carbon ion boost followed by IMRT). Details on the statistical design, study population as well as the inclusion and exclusion criteria were previously reported [18]. Human papilloma virus (HPV) status is not available in the cohort.

The treatment was as follows: patients were planned to receive 3 cycles of docetaxel/cisplatin/5-FU (TPF; Docetaxel 75 mg/m^2 BSA (d1, d22, d43), Cisplatin 75 mg/m^2 BSA (d1, d22, d43), 5-FU 750 mg/m^2 (d1-5, d22-26, d47-51)) afterwards, monoclonal antibody therapy (administered according to market authorization) with cetuximab was performed concurrently to radiotherapy: 1st infusion 400 mg/m^2 BSA followed by weekly doses of 250 mg/m^2 BSA in rate-controlled intravenous infusions. Schedule of administration: d58, d65, d72, d79, d86, d93, d100, d107. The radiotherapy applied first a carbon ion boost (24Gy(RBE) in 8 fractions 3Gy(RBE)

Table 1
Inclusion and exclusion criteria of the TPF-C-HIT trial.

1.1 Inclusion criteria
1. Signed written informed consent
2. Age of 18 to 70 years
3. Life expectancy of at least 6 month
4. Ability of subject to understand character and individual consequences of clinical trial
5. Histologically confirmed locally advanced (stage III or IV), non-metastatic squamous cell carcinoma of the oro-, hypopharynx and larynx (T2-4, any N,M0)
6. Oral cavity or oro- , hypopharynx or larynx as the primary tumor site
7. At least one uni-measurable lesion according to the RECIST criteria
8. Karnofsky Performances Status ≥70%
9. Adequate bone marrow function: neutrophils > 1.5 x 10^9/L, platelets > 100 x 10^9/L, hemoglobin > 10.0 g/dL
10. Until amendment 1 IC10: Adequate liver function: Bilirubin < 2,0 g/dL, SGOT, SGPT <3 x ULN
Since Amendment 1: Adequate liver function: Bilirubin <1,5 mg/dL, SGOT, SGPT <3 x ULN, GGT < 5x ULN
11. Until amendment 1: Adequate renal function: Serum creatinine <1.5 mg/dL
Since Amendment1: Adequate renal function: GFR >70 ml/min
12. Negative serum/urine Beta-HCG test in women of childbearing potential,
13. Women of childbearing potential: willingness to use effective contraceptive method, defined as the concomitant use of either an intrauterine pessary (IUP) or contraceptive pill and in both cases, condoms for the treatment duration and 2 months thereafter. Women of non-childbearing potential are those who are post-menopausal for at least 1 year or sterilized,
14. Men of procreative potential: willingness for effective prevention of procreation, defined as a use of condoms and a use of an intrauterine pessary (IUP) or a contraceptive pill by his partner for the treatment duration and 2 months thereafter,
15. Subject's consent to collect blood samples (and/ or tumor tissue since amendment 1) for proteomics and genomics analysis. If a patient does not consent, no samples for proteomics and genomics will be taken. Nonetheless, he/she may be enrolled in the study.

1.2 Exclusion criteria
1. Previous systemic chemotherapy, radiotherapy or surgery for carcinoma of the head and neck
2. Nasopharyngeal Carcinoma
3. Prior exposure to EGFR pathway targeting therapy
4. Other serious illness or medical conditions:
   - Unstable cardiac disease despite treatment, congestive heart failure NYHA grade 3 and 4
   - Significant neurologic or psychiatric disorders including dementia or seizures,
   - Active disseminated intravascular coagulation
   - Other serious underlying medical conditions which in the opinion of investigator could impair the ability of the patient to participate in the study
   - Symptomatic peripheral neuropathy Common Toxicity Criteria (CTC) grade 2 or higher
   - Ototoxicity CTC grade 2 or higher, except if due to trauma or mechanical impairment due to tumor mass
5. Participation in other interventional trial within the last 30 days
6. Surgery within the last 30 days
7. Known allergic/hypersensitivity reaction to any drugs scheduled for the study treatment
8. Women: pregnant or breast-feeding
9. Known drug abuse
10. Other previous malignancy within 5 years, with exception of a history of a previous, adequately treated, basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix
11. Legal incapacity or limited legal capacity
12. Medical or psychological condition which in the opinion of the investigator would not permit the patient to complete the study or sign meaningful informed consent

each) to the primary tumor and pathologic lymph nodes followed by IMRT (50 Gy (±5%) in 25 fractions 2 Gy each) to the primary tumor, pathologic lymph nodes and elective lymph node levels. The in- and exclusion criteria were presented in Table 1.

The study was designed as a prospective, mono-centric, open-label, non-randomized phase II trial with a single treatment group. A flow-chart reflecting the study procedures is seen in Fig. 1. The study was sponsored by the Heidelberg University Hospital and approved by the local ethics committee as well as competent higher federal authority (Paul-Ehrlich-Institute). The EudraCT number is 2009-016489-10. The independent contract research organization Alcedis GmbH (Gießen, Germany) was contracted to support study conduct. All patients gave informed consent to participate in the study.

The primary endpoint of this study was the local-regional control (LRC) after 1 year. The secondary endpoints were disease-free survival (DFS), progression-free survival (PFS), overall survival (OS), acute radiation effects, late radiation effects, adverse events and quality of life according to EORTC QLQ-C30 at 12 months.

The study was terminated early because of slow accrual. Reasons for the slow accrual were on the one hand the moderate patient numbers seen in our interdisciplinary ENT clinic and on the other hand the in- and exclusion criteria in combination with the patient cohort presenting in our interdisciplinary ENT clinic. Furthermore, coverage of the treatment costs had to be individually obtained from the patients insurance companies.

The study follow-up visits were scheduled including MRI and clinical examination 6–8 weeks after end of radiotherapy, 3 months thereafter, 6 months and 12 months.

3. Results

Between Q4 2010 and Q3 2012 a total of 8 patients were enrolled into the trial. Median patient age was 52.5 years (44–67 years). The median duration of the therapy was 106 days (57–113). The median trial follow-up was 13.5 months (12–14 months). Further patient characteristics were found in Table 2.

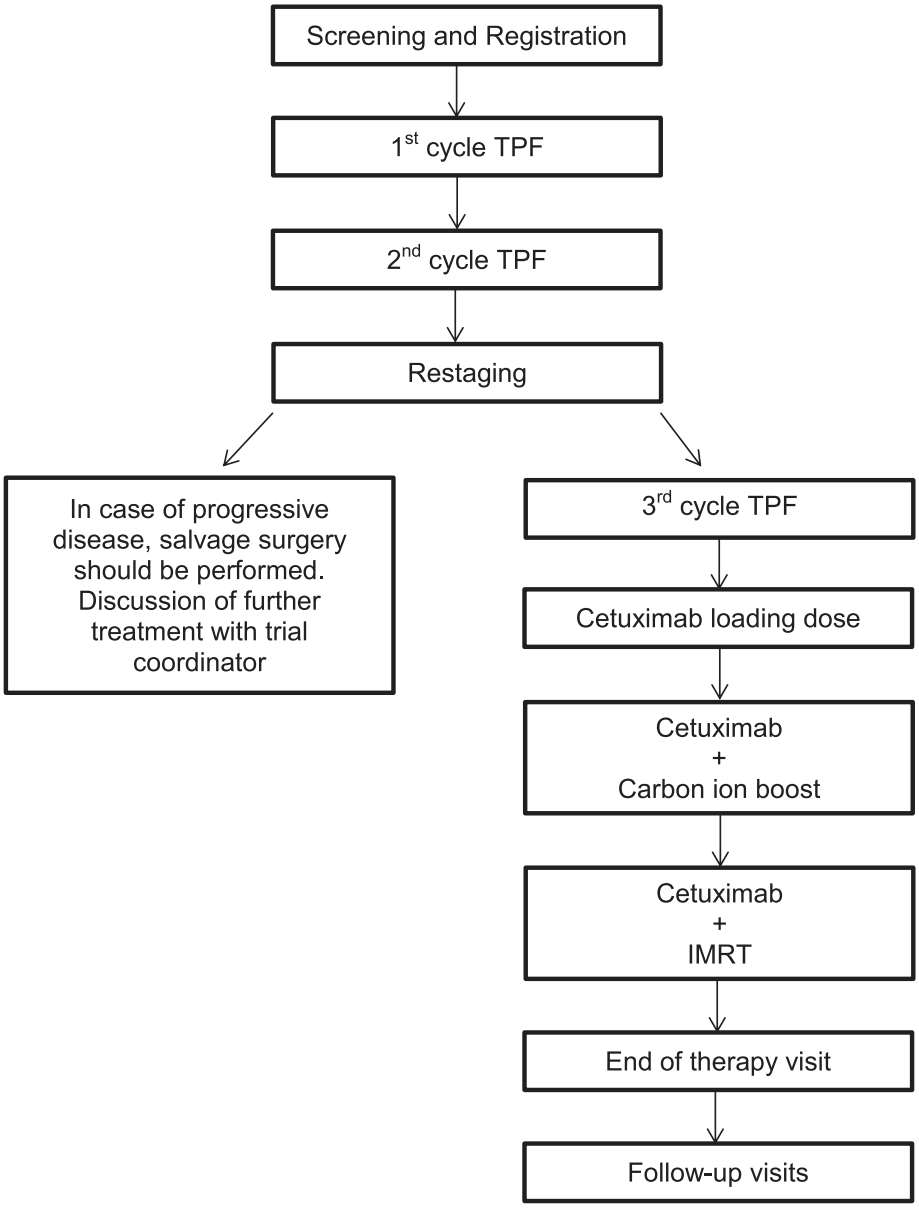

Fig. 1. Flow-chart of the TPF-C-HIT trial.

Table 2
Patients' characteristics.

Parameter	N	%
Gender		
Male	5	62.5
Female	3	37.5
Tobacco consumption		
Yes	4	50
No	4	50
Alcohol consumption		
Yes	3	37.5
No	5	62.5
Localization		
Oropharynx	5	62.5
Larynx	1	12.5
Hypopharynx	1	12.5
Oral cavity	1	12.5
Grading		
G1	0	0.0
G2	4	50
G3	4	50
T-stage		
T1	0	0.0
T2	1	12.5
T3	2	25
T4a	4	50
T4b	1	12.5
N-stage		
N1	0	0.0
N2a	0	0.0
N2b	5	62.5
N2c	3	37.5
N3	0	0.0
M-stage		
M0	8	100
Stage		
III	1	12.5
Iva	6	75
Ivb	1	12.5

3.1. Compliance with protocol

3.1.1. TPF induction chemotherapy

The median total dose of docetaxel and cisplatin was identical for both substances and amounted to 141 mg at cycle 1 and to 131.5 mg at cycles 2 and 3. The median total dose of 5-FU amounted to 7050 mg at cycle 1 and 6575 mg for cycles 2 and 3. The reason for dose modification was hematological toxicity. The most common concomitant therapies were antibiotics and G-CSF. Additionally no patient discontinued study after chemotherapy cycles.

3.1.2. Cetuximab

The median dose of cetuximab was 400 mg/m^2 BSA at week 9. In weeks 10–16 the median cetuximab dose amounted to 250 mg/m^2 BSA. There was no dose modification during cetuximab therapy. One patient discontinued therapy after week 9 and one patient after week 16, respectively.

3.1.3. Carbon ion boost

Patients received carbon ion therapy on 6 subsequent working days (Tuesday through Saturday) in doses of 3Gy(RBE) per fraction to a total dose of 24Gy(RBE).

3.1.4. Intensity-modulated radiotherapy (IMRT)

IMRT was planned and administered following the carbon ion boost without any delays at the next working day in 2 Gy per fraction to a total dose of 50 Gy per fraction (±5%). Cumulative dose of the radiotherapy treatment was 74 Gy(RBE). No dose modifications during radioimmunotherapy were conducted.

3.2. Tumor control

None of the patients was diagnosed with locoregional progression; therefore the locoregional tumor control rate was 100.0% at 12 months. During the further follow-up after the study time, 2 patients were diagnosed with local recurrence at 20 and 23 months after end of therapy. In one case recurrence was associated with mandibular osteonecrosis. Best treatment response during the 12-months study follow-up was complete remission in 7 patients (87.5%) and partial remission in 1 patient (12.5%). None of the patients showed distant failure. The 12-months progression-free survival and overall survival rate were 100.0% each.

3.3. Radiation-associated adverse events (AE)

Radiation-associated early and late AE in this study have been mainly mucositis, dermatitis, dysphagia and xerostomia. Details on radiation-related AE are shown in Table 3a. The most commonly documented late AE was xerostomia, which has been documented in 100.0% of the patients up to the 9 months follow-up visit. At the 12 months follow-up visit still 85.7% of the patients had xerostomia.

3.4. Therapy-associated adverse events

A total of 203 AE occurred in 8 patients from the first day of therapy until the last follow-up visit. Oral mucositis was the most commonly documented AE (13.5% of all AEs), followed by decreased white blood cells (6.4%) and decreased neutrophil count (4.9%). AE according to NCI with a total prevalence >1% are listed in Table 3b. Recovery was seen for 73.4% of the AE and

Table 3a
Radiation-associated adverse events documented by ear-nose-throat examinations.

Adverse events		Pre-examination		End of therapy		Month 3		Month 6		Month 9		Month 12	
		N	%	N	%	N	%	N	%	N	%	N	%
Mucositis	No	8	100.0	3	37.5	4	50.0	7	87.5	7	100.0	7	100.0
	Yes	0	0.0	5	62.5	4	50.0	1	12.5	0	0.0	0	0.0
Dermatitis	No	8	100.0	8	100.0	7	87.5	8	100.0	7	100.0	7	100.0
	Yes	0	0.0	0	0.0	1	12.5	0	0.0	0	0.0	0	0.0
Dysphagia	No	7	87.5	5	62.5	4	50.0	5	62.5	5	71.4	6	85.7
	Yes	1	12.5	3	37.5	4	50.0	3	37.5	2	28.6	1	14.3
Xerostomia	No	8	100.0	0	0.0	0	0.0	1	12.5	0	0.0	1	14.3
	Yes	0	0.0	8	100.0	8	100.0	7	87.5	7	100.0	6	85.7

Table 3b
Therapy-associated adverse events according to NCI CTCAE Version 4.0 (limited to total prevalence >1%).

NCI grade	Grade 1	Grade 2	Grade 3	Grade 4	Total N	Total %
Abdominal pain	2	0	0	0	2	1.8
Constipation	3	1	0	0	4	3.6
Cough	2	1	0	0	3	2.7
Diarrhea	3	1	0	0	4	3.6
Dry mouth	1	1	0	0	2	1.8
Dry skin	3	0	0	0	3	2.7
Dysphagia	1	2	1	0	4	3.6
Erythema multiforme	1	1	0	0	2	1.8
Fatigue	0	2	0	0	2	1.8
Fever	2	0	0	0	2	1.8
Gastrointestinal disorders – Other	0	3	0	0	3	2.7
Hypokalemia	1	0	1	0	2	1.8
Hypomagnesemia	2	0	0	0	2	1.8
Infections and infestations – Other	0	1	1	0	2	1.8
Mucositis oral	0	3	4	0	7	6.3
Nausea	1	0	1	0	2	1.8
Neutrophil count decreased	0	2	3	3	8	7.2
Pharyngitis	0	2	0	0	2	1.8
Rash acneiform	2	1	0	0	3	2.7
Rash maculo-papular	1	1	0	0	2	1.8
Skin and subcutaneous tissue disorders – Other	3	2	0	0	5	4.5
Stomach pain	2	0	0	0	2	1.8
Tinnitus	1	1	0	0	2	1.8
Watering eyes	2	0	0	0	2	1.8
Weight loss	2	0	0	0	2	1.8
White blood cell decreased	1	2	4	0	7	6.3

no AE resulted in death. One AE was the reason for the end of therapy.

A total of 5 serious adverse events (SAE) were documented in 4 patients. In 2 patients mucositis NCI grade 3 and in one case a decreased lymphocyte count grade 4 were found. Febrile neutropenia (grade 4) leading to dose reduction of chemotherapy and hypersensitivity (grade 3) related to cetuximab leading to withdrawal of cetuximab treatment had occurred in 1 patient each. All of the documented SAE did recover.

3.5. EORTC QLQ-C30 questionnaires

Most of the symptom scale scores of the EORTC QLQ-C30 questionnaire had their worst mean value at the last day of therapy (day 109; fatigue, nausea and vomiting, pain, dyspnea, appetite loss, constipation). Nausea, vomiting and constipation were transient showing recovery not later than the 4th follow-up visit. Sleep disturbances and concerns about the financial impact of the therapy have been found frequently and have not completely attained baseline level. Details are shown in Figs. 2 and 3a, b.

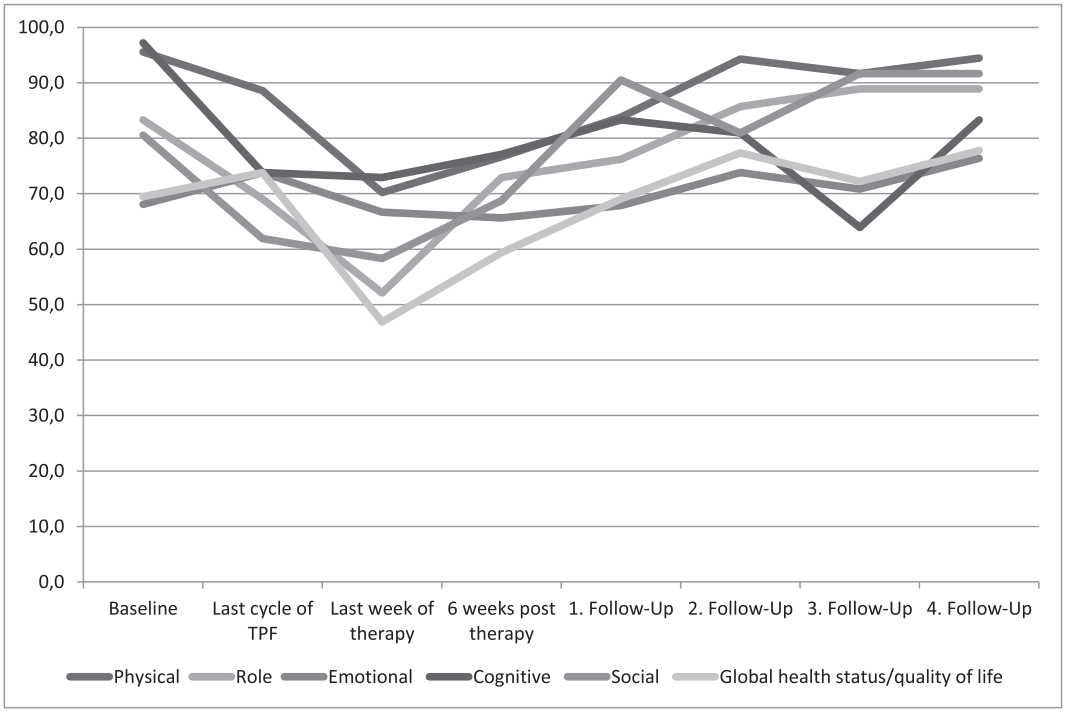

Fig. 2. EORTC-QLQ-C30 Questionnaire functional results (mean values) at baseline, last cycle of TPF, last week of therapy, 6 weeks post therapy, 1. Follow-up (3 months), 2. Follow-up (6 months), 3. Follow-up (9 months) and 4. Follow-up (12 months).

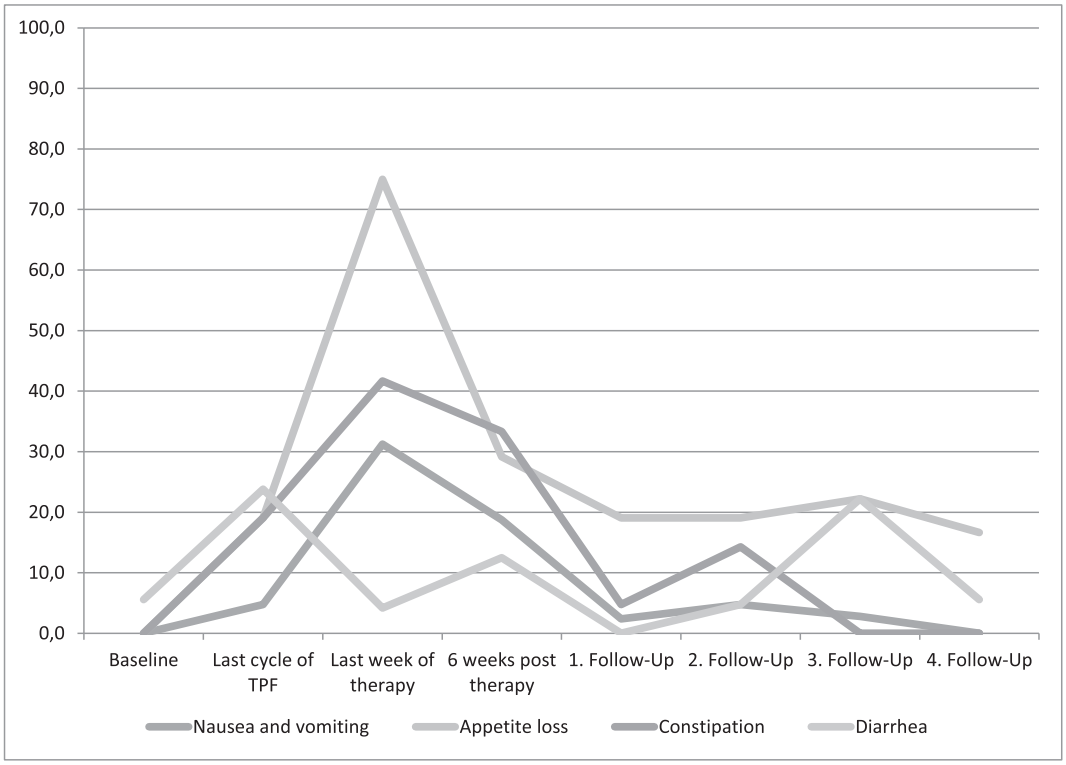

Fig. 3a. EORTC-QLQ-C30 Questionnaire gastrointestinal symptom scales (mean values) at baseline, last cycle of TPF, last week of therapy, 6 weeks post therapy, 1. Follow-up (3 months), 2. Follow-up (6 months), 3. Follow-up (9 months) and 4. Follow-up (12 months).

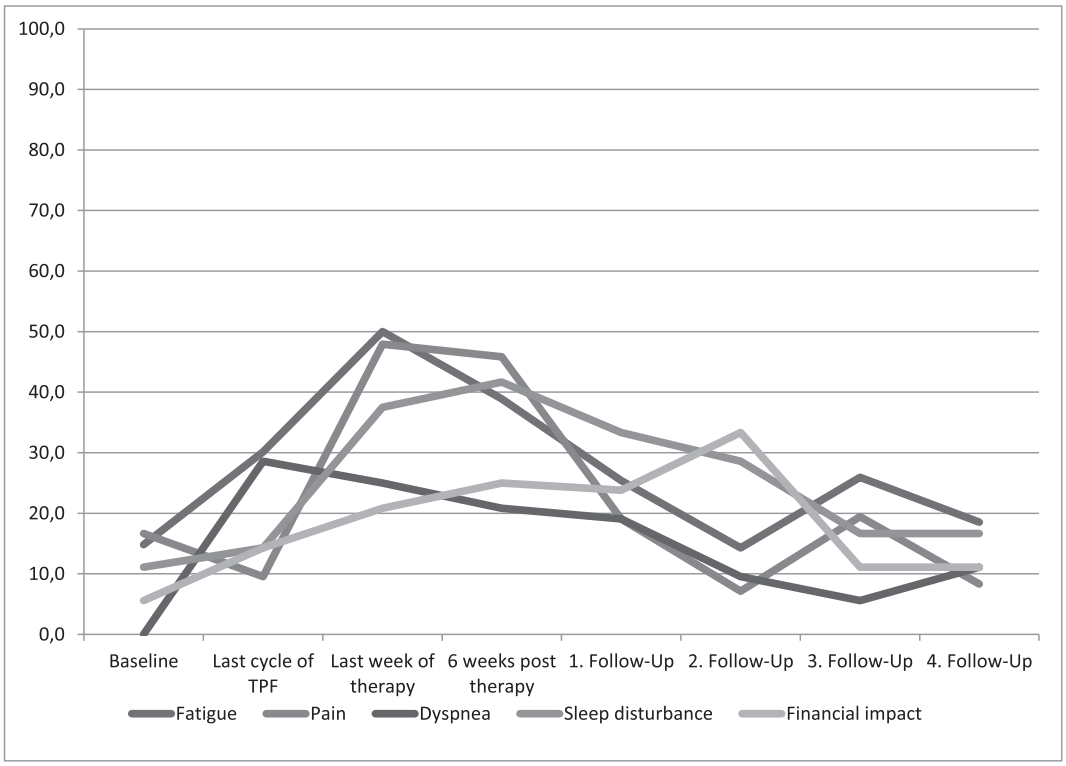

Fig. 3b. EORTC-QLQ-C30 Questionnaire non-gastrointestinal symptom scales (mean values) at baseline, last cycle of TPF, last week of therapy, 6 weeks post therapy, 1. Follow-up (3 months), 2. Follow-up (6 months), 3. Follow-up (9 months) and 4. Follow-up (12 months).

3.6. EORTC QLQ H&N 35 questionnaires

All but one of the multi-item symptom scale scores (pain, swallowing, speech problems, trouble with social eating, trouble with social contact and less sexuality) had their worst outcome on the last day of therapy (day 109). The high intensity of these symptom scales was transient with mean values recovered to baseline at the 4th follow-up visit. Regarding the single-item symptom scale scores, some symptom items (coughing, feeling ill) had transiently deteriorated. The symptoms dry mouth and sticky saliva had their worst outcome at the end of therapy or 6 weeks after and were not completely resolved at 12 months. An increased value of teeth problems and the use of a feeding tube might be the result of salivary gland impairment. Also weight loss has been reported from day 43 to the 2nd follow-up visit. Details regarding the single-item symptom scale scores are shown in Figs. 4a–c.

4. Discussion

In this prospective, mono-centric, open-label, non-randomized phase II trial the efficacy and safety of the combined treatment with IMRT/carbon ion boost and weekly cetuximab following TPF induction in patients with locally advanced SCCHN was evaluated.

Despite intensive local treatment, prognosis and clinical outcome for patients with advanced SCCHN is poor. Chemoradiation leads to increased toxicities [19] therefore other treatment strategies need to be evaluated in order to improve outcome as well as toxicity, quality of life and compliance. The TPF-C-HIT trial combines treatment with the EGFR-antibody cetuximab and novel radiotherapy techniques (IMRT and carbon ions boost) following TPF induction chemotherapy.

Addition of docetaxel to standard induction chemotherapy with cisplatin and fluorouracil has been shown to improve PFS and OS [6,7]. In view of the high expression of EGFR in SCCHN, targeted therapies including monoclonal antibodies against EGFR are an appealing treatment. High expression of this growth factor receptor is associated with increased tumor size, decreased radiation sensitivity, and increased risk of recurrence [10,11]. Meanwhile refined radiotherapy techniques such as IMRT have become standard therapeutic approaches in the treatment of head and neck cancer.

However, particle beam therapies offer further improvements in for example organ at risk (OAR) sparing or conformity [20]. Amirul Islam et al. were able to show in an in-silico study that carbon ion radiotherapy improved conformity and OAR sparing compared to 3D conformal radiotherapy as well as IMRT [21]. In addition, advanced SCCHN may have factors causing relative radio-resistance such as tumor hypoxia [22]. Moncharmont et al. concluded in their work on carbon ions and cancer stem cells in SCCHN that carbon ions are a promising approach counteracting the migration and invasion process in paternal and cancer stem cells [17]. Therefore, carbon ions might be able to overcome different factors causing relative radio-resistance and thereby improve oncologic outcome.

In none of our patients death or disease progression occurred during the treatment and study follow-up period. Locoregional control rate at 12 months, which was the primary endpoint, was 100%. In the study of Posner et al. patients with unresectable squamous cell carcinoma of the oral cavity, larynx, oropharynx, and hypopharynx (stage III or IV) received TPF (PF) induction therapy followed by chemoradiation showing an OS of approximately 85% (70%) and PFS of approximately 65% (55%) at 12 months [6]. Therefore, OS and PFS rates of 100% at the 12 months follow-up visit in the TPF-C-HIT study seem to be superior. However, results are not directly comparable due to a different patient population and small sample size of the TPF-C-HIT study. In a recent report

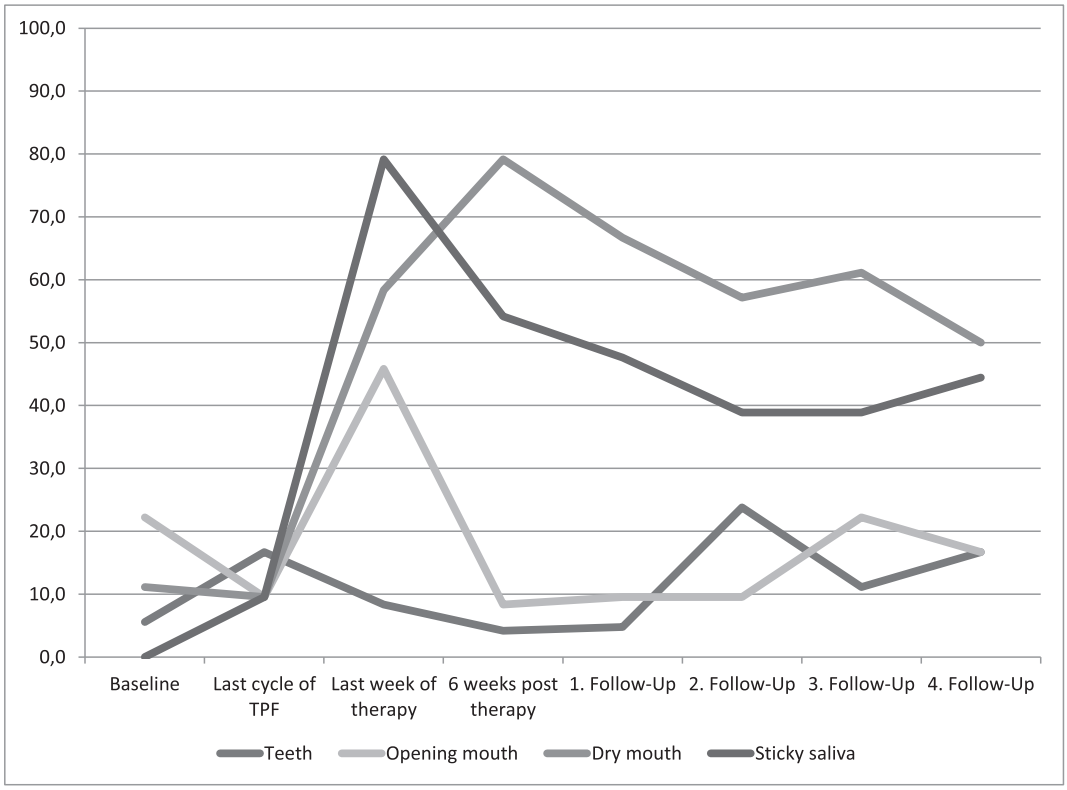

Fig. 4a. EORTC QLQ H&N 35 single item scale scores (oral part, mean values) at baseline, last cycle of TPF, last week of therapy, 6 weeks post therapy, 1. Follow-up (3 months), 2. Follow-up (6 months), 3. Follow-up (9 months) and 4. Follow-up (12 months).

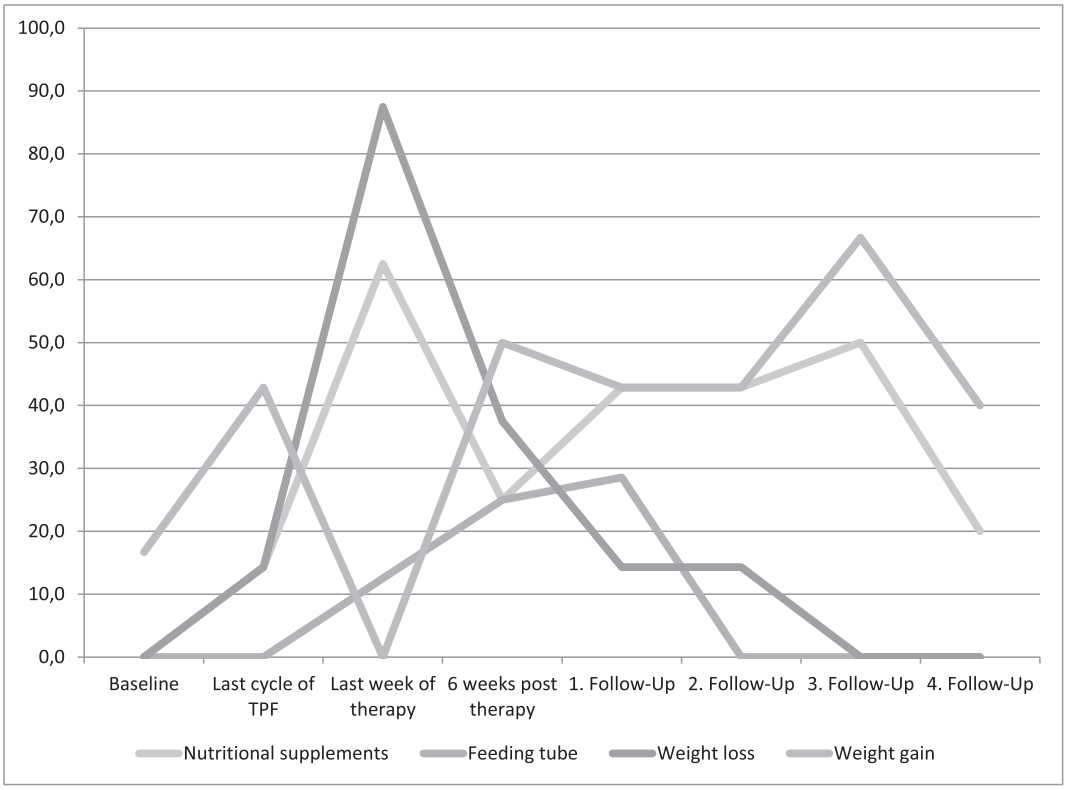

Fig. 4b. EORTC QLQ H&N 35 single item scale scores (gastrointestinal, mean values) at baseline, last cycle of TPF, last week of therapy, 6 weeks post therapy, 1. Follow-up (3 months), 2. Follow-up (6 months), 3. Follow-up (9 months) and 4. Follow-up (12 months).

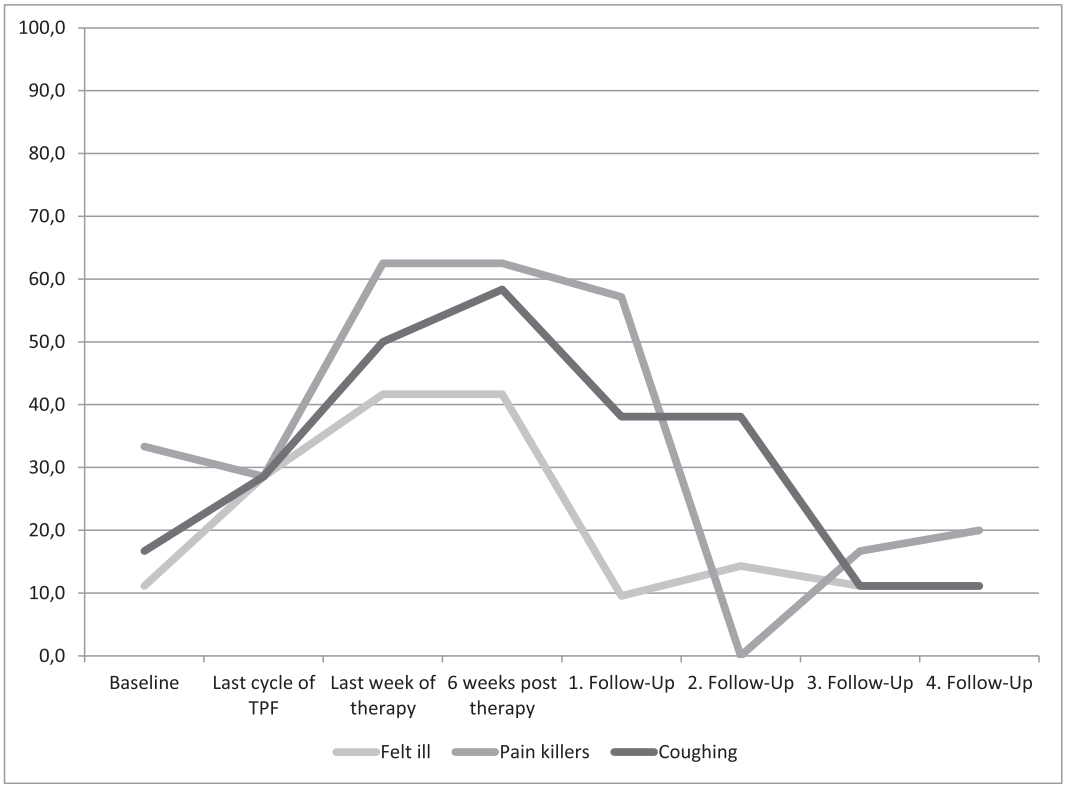

Fig. 4c. EORTC QLQ H&N 35 single item scale scores (other symptoms, mean values) at baseline, last cycle of TPF, last week of therapy, 6 weeks post therapy, 1. Follow-up (3 months), 2. Follow-up (6 months), 3. Follow-up (9 months) and 4. Follow-up (12 months).

by Koto et al. on carbon ion radiotherapy in SCC of the middle ear, the 1-year LC was 72%. Mizoe et al. reported besides others a 5-year LC of 61% in patients with SCC of the head and neck treated with carbon ions [23]. Ten percent of Mizoes patients developed grade 3 mucositis or dermatitis and the authors specified that no serious adverse events related to carbon ions were found during follow-up. Due to the shorter follow-up in our trial a comparison is difficult, however, a low rate of high-grade AE related to carbon ions was seen in our trial, too. The 12-months OS and LC were with approximately 70% and approximately 50% in the GORTEC 2007-002 trial lower than in our trial with 100% each [13]. This difference might be due to for example patient selection, the low patient number in our trial or the different biological effects of the carbon ion boost.

Regarding the safety, a total of 203 AE occurred in the 8 included patients. 73.4% of the AE were recovered and no AE resulted in death. Furthermore, 42.9% of the AE required therapy and 2.5% were regarded as serious. All of the 5 SAEs were recovered but one SAE resulted in dose reduction and one in a withdrawal of the treatment. Reasons for SAE were hospitalization/prolongation in 4 cases and other medically important reasons in 1 case. In 2 cases (mucositis) the respective SAE was documented to be directly related to cetuximab and radiotherapy. Comparing our results with GORTEC 2007-002 the results regarding AE are inhomogeneous [13]. In contrast to GORTEC there were no treatment related deaths in our cohort and for example grade 3–4 neutropenia (fever) was found in GORTEC in 26% (9%) and in 75% (0%) in our cohort. However, grade 3–4 mucositis was comparable between GORTEC (50%) and our cohort (50% grade 3) as well as relatively low rates of hypersensitivity reactions to cetuximab (GORTEC 7% versus 12,5% in our cohort).

Concerning the impact of therapy on patient's quality of life assessed by EORTC QLQ-C30 questionnaire, all of the functional scales worsened during therapy but the majority of the functional scale scores recovered to baseline levels at the end of the follow-up period. Cognitive function was slightly reduced at the end of follow-up compared to baseline level. Also for the symptom scales scores worsening was recognized during therapy. Symptoms like dyspnea and appetite loss occurred during therapy and persisted during the follow-up period. Some ear-nose-throat (ENT) symptoms were diagnosed after therapy and during follow-up period. In 1 patient dysphagia had not recovered and in 6 patients (85.7%) xerostomia was persistent at the end of follow-up. Xerostomia is a major source for chronic morbidity after radiation therapy and may impair QoL. The long term effects of xerostomia include subsequent weight loss, dental decay and chronic infection of the oral cavity [24].

Assessment of QoL by using the head and neck cancer specific module EORTC H&N 35 also showed a decreased quality of life during therapy concerning all symptom scales. However, all but one symptom scale (sense problems) had recovered until the 4th follow-up visit. As already indicated by assessment of ENT examinations, the results of H&N35 assessment imply an at least longer term impairment of salivary gland function which led to problems with teeth and functional and social eating.

5. Conclusion

The trimodal therapeutic approach used in the present study was tolerable and promising for patients with locally advanced squamous cell carcinoma of the oro-, hypopharynx and larynx. QoL was obviously reduced during therapy but had recovered for most of the aspects until the last follow-up visit. However, impairment of salivary gland function of some degree is indicated by QoL questionnaires. Due to the low number of patients and a relatively short follow-up period, the efficacy results of the TPF-C-HIT are difficult to compare with results of other studies. Further research is warranted to determine the value of carbon ions in advanced head and neck squamous cell carcinoma.

Conflict of interest

Hartmann S. and Windemuth-Kieselbach C. declare that they are employed by Alcedis, a CRO and therefore work for different academic and commercial sponsors.

The other authors declare to not have conflicts of interest.

Role of the funding source

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