

ORIGINAL ARTICLE

TPF plus cetuximab induction chemotherapy followed by biochemoradiation with weekly cetuximab plus weekly cisplatin or carboplatin: a randomized phase II EORTC trial

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Background: Our aim was to test the safety of cetuximab added to chemoradiation with either cisplatin or carboplatin after prior induction chemotherapy.

Methods: Patients with stage III/IV unresectable, squamous cell carcinoma of the head and neck received up to four cycles of TPF-E (cisplatin and docetaxel 75 mg/m² on day 1 followed by 5-FU 750 mg/m²/day as a continuous infusion on days 1–5 plus cetuximab at a loading dose of 400 mg/m² followed by a weekly dose of 250 mg/m²), with prophylactic antibiotics but no growth factors. Patients not progressing after four cycles of TPF-E were randomly assigned to radiotherapy (70 Gy over 7 weeks in 2 Gy fractions) and weekly cetuximab with either weekly cisplatin 40 mg/m² or carboplatin, AUC of 1.5 mg/ml/min. Primary endpoint was feasibility.

Results: Forty-seven patients were recruited. One patient did not start TPF (hypersensitivity reaction during the cetuximab loading dose). Induction TPF-E was discontinued in 12 patients due to toxicity (6 patients), medical decision (2), death (1), patient refusal (1), protocol violation (1), co-morbidity (1). Three further patients were not randomized [progressive disease (1), protocol violation (1), toxicity and co-morbidity (1)]. Of particular interest are three patients who suffered from bowel perforation, one patient who died as results of pneumonia and septic shock, and a second patient who was found dead at home 12 days after starting TPF-E (cause of death unknown). Weekly cisplatin and carboplatin was stopped early in seven and four patients, respectively. Radiotherapy was stopped in two patients with cisplatin and interrupted in one patient with cisplatin and four patients with carboplatin.

Conclusions: The addition of cetuximab to full dose TPF induction chemotherapy led to unacceptable complications and premature closing of the study. Only 34 out of 46 patients completed four cycles of TPF-E and only 30 started biochemoradiation.

Key words: head and neck cancer, locoregionally advanced, induction chemotherapy, cetuximab, biochemoradiation, TPF

Introduction

Standard treatment options for patients with locoregionally advanced non-metastatic (stage III or IV) squamous cell carcinoma of the head and neck (LA-SCCHN) include surgery followed by

postoperative (chemo)radiation and definitive cisplatin-based chemoradiation [1]. The addition of cetuximab to irradiation (bioirradiation) is also associated with a significant improvement in locoregional control and overall survival (OS) [2, 3]. The role of

induction chemotherapy remains highly controversial [4–6]. The addition of a taxane to the combination of cisplatin and 5-fluorouracil (PF) consistently improved the outcome in randomized phase 3 trials [7]. The updated meta-analysis of chemotherapy in head and neck cancer (MACH-NC) suggested that induction chemotherapy and concomitant chemoradiotherapy might have complimentary effects on disease control [8]. We hypothesized that the addition of cetuximab to induction chemotherapy and chemoradiation might further improve the outcome. In order to test the feasibility and safety of such an approach, we conducted a randomized phase II trial in which two platinum-based strategies in sequential design were studied in order to select one to be used as experimental arm in a future phase III trial.

Methods

Study population

Eligibility criteria included histologically proven newly diagnosed stage III or IV unresectable non-metastatic measurable SCCHN, World Health Organisation (WHO) performance status (PS) 0 or 1, age 18–75 years, and adequate organ functions. All patients gave written informed consent. Excluded were patients with nasal, paranasal, or nasopharyngeal primaries, and patients with a history of other malignancy.

Baseline evaluation included medical history, physical examination, vital signs, WHO PS, complete blood counts, serum chemistry, urinalysis, gadolinium-enhanced magnetic resonance imaging (MRI) or contrast computed tomography (CT)-scan of the head and neck, chest X-ray with or without CT-scan, endoscopy, abdominal ultrasound or CT-scan in case of liver function test abnormalities, bone scan in case of local symptoms, electrocardiogram (ECG) and left ventricular ejection fraction (LVEF) assessment, and a baseline formalin-fixed paraffin-embedded (FFPE) tumor sample.

Treatment

Induction chemotherapy. Patients were scheduled to receive two cycles of TPF-E every 3 weeks (cisplatin 75 mg/m² and docetaxel 75 mg/m² on day 1 followed by 5-FU 750 mg/m²/day as a continuous infusion days 1–5) followed by two additional TPF-E cycles in the absence of disease progression (PD). Prophylactic antibiotic therapy was mandatory. Ciprofloxacin (or an alternative) was recommended at 500 mg orally bid for 10 days starting on day 5 of each cycle.

No primary prophylactic administration of granulocyte colony stimulating factor (G-CSF) was permitted. However, G-CSF was to be given prophylactically during the second and/or subsequent cycles in patients with febrile neutropenia or infection, delayed recovery of absolute neutrophil count at day 28, or grade 4 neutropenia persisting for ≥7 days during a prior cycle.

In case of progression at any time during induction chemotherapy patients went off-study.

Concurrent chemoradiotherapy. At the end of induction chemotherapy, patients with stable disease (SD), partial (PR) or complete response (CR) were randomized to receive either cisplatin 40 mg/m² or carboplatin AUC 1.5 mg/ml/min, administered weekly for the entire duration of the RT. Conventionally fractionated radiotherapy (70 Gray [Gy] over 7 weeks in 2 Gy fractions) was to be started within 5 weeks from the start of the last TPF-E cycle. Standard opposed fields with a single anterior field as well as conformal techniques (3D-conventional radiotherapy and/or intensity modulated RT [IMRT]) were allowed. A simultaneous integrated boost (SIB) technique was not allowed.

Cetuximab treatment. Cetuximab was started at a loading dose of 400 mg/m² on day 1 of the first induction TPF-E cycle and thereafter administered weekly at a dose of 250 mg/m² throughout the entire treatment period (during induction chemotherapy and concurrent chemoradiotherapy).

Assessments

Physical examination including vital signs, and neurological evaluation, toxicity scoring according to CTCAE 3.0, and complete blood counts and serum chemistry were performed weekly. At the end of TPF-E cycle 2 and 4 and 3 months after end of concurrent chemoradiation, a gadolinium-enhanced MRI or CT scan of the head and neck was performed. ECG, LVEF assessment, and endoscopy were mandatory at the end of TPF-E cycle 4.

Study design

This was a randomized, open label, multi-center, phase II screening feasibility trial.

Random treatment allocation was stratified by institution and by response to TPF-E (response versus non-response).

The primary endpoint was feasibility of the chemoradiotherapy part of the treatment, defined as at least 80% dose intensity of any of the RT, the platinum and cetuximab during that part of the treatment protocol. In order for a patient to be classified into the category where the regimen was feasible, all of the following were to be satisfied: at least 66 Gy of RT received, at least 80% relative dose intensity of RT, at least 80% relative dose intensity of the platinum (cisplatin or carboplatin) during the biochemoradiation, at least 80% relative dose intensity of cetuximab during biochemoradiation.

Any case not satisfying these criteria was counted as failing the feasibility criterion. Secondary endpoints were toxicity, dose modifications, and response rate (CR and PR).

Statistical design and analysis

The trial aimed to detect a treatment arm that had a feasibility rate of 80% among patients that could proceed to biochemoradiation. For this feasibility rate, 60% was chosen as a rate of little interest. A Sargent and Goldberg design was used. If one arm had the desired feasibility rate (80%) and the other arm had the rate of little interest (60%), there would be a 90% probability of selecting the better arm. This could be achieved by randomizing 25 patients per arm, and selecting the arm that had at least a 7% superior feasibility rate (corresponding to two more patients with feasible chemoradiotherapy out of 25). If the difference was <7%, the selection had to be done according to other data, and it was assumed that in half of those cases the better arm would be chosen. If the two arms in reality had similar (but different) feasibility rates, the probability of choosing the worse arm was >10%. If the worst arm had a primary endpoint rate of 65% (versus 80%), then the probability of selecting the better arm was >85%.

Randomization was restricted to non-progressive patients after TPF-E. Assuming a drop-out of 10% for not reaching chemoradiotherapy, 55 patients were expected to be enrolled.

The analysis of the primary endpoint was to be conducted on the set of patients randomized into the biochemoradiation part of the study who started their allocated treatment (at least one dose of the platinum). Patients who dropped out due to toxicity or patient decision were to be counted into this population, as failures. Feasibility rates by treatment arm, with two-sided 95% exact confidence intervals were to be calculated. No direct comparisons between treatment arms other than the decision rule of the Sargent and Goldberg design were planned. Tolerability and safety were described using CTCAE 3.0 grade.

Results

Between April 2008 and December 2009, 47 patients from seven institutions in Italy, Hungary, the Netherlands, and Belgium were recruited. One patient did not start TPF due to a hypersensitivity reaction during the cetuximab loading dose. The EORTC Independent Data Monitoring Committee (IDMC) recommended definitive closure of the study in May 2010 because of safety concerns during the induction part of the study.

Of the 47 patients recruited, 31 were randomized to receive either cisplatin-based ($n = 15$) or carboplatin-based ($n = 15$) biochemoradiation (see CONSORT flow chart, supplementary Figure S1, available at *Annals of Oncology* online). Baseline characteristics of the patients are shown in Table 1.

Compliance and safety during induction chemotherapy

Thirty-four (73.9%) patients received 4 cycles of TPF-E, while 4 (8.7%), 6 (13%), and 2 (4.3%) patients received 3, 2, or 1 cycle, respectively. Treatment duration and dose intensity are summarized in Table 2. Median relative dose intensity was 97.6% for TPF-E and 102.2% for cetuximab. TPF-E dose and schedule modifications are summarized in the supplementary Table S1, available at *Annals of Oncology* online. TPF-E was discontinued in 12 patients. Reasons for discontinuation were toxicity ($n = 6$;

1 grade 5 [febrile neutropenia, and septic shock]), protocol violation ($n = 1$), patient's best interest ($n = 2$), patient refusal ($n = 1$), death of unknown cause after the first TPF-E cycle ($n = 1$), cerebrovascular accident ($n = 1$). Three further patients were not randomized due to PD under TPF-E ($n = 1$), protocol violation ($n = 1$), and co-morbidity and toxicity issues ($n = 1$). Grade ≥ 3 toxicity during TPF-E is summarized in the supplementary Table S2, available at *Annals of Oncology* online. Of particular interest are three patients who suffered from bowel perforation, one patient who died as results of pneumonia and septic shock and a second patient who was found dead at home 12 days after starting treatment with TPF-E (cause of death unknown).

Compliance and safety during chemoradiotherapy

Of the 31 patients randomized, one patient allocated to the cisplatin arm did not start biochemoradiation for toxicity reasons. One patient allocated to the carboplatin arm did not receive cetuximab during biochemoradiation (hypersensitivity reaction during induction phase). Adherence to protocol-specified therapy during biochemoradiation is summarized in Supplementary Table S3, Available at *Annals of Oncology* online.

Dose intensity is summarized in Table 3. Cisplatin and carboplatin were stopped prematurely in seven (46.7%) and four (26.6%) patients, respectively. Cetuximab was stopped early in four patients (26.6%) of the carboplatin arm because of skin

Table 1. Patient characteristics

	All patients	TPF safety population	Chemoradiation safety population		
	<i>n</i> =47	<i>n</i> =46	Cisplatin <i>n</i> =15	Carboplatin <i>n</i> =15	Total <i>n</i> =30
Age (years)					
Median	56.7	57	56.7	55.7	56.2
Range	48.5–71.8	48.5–71.8	48.5–68.7	48.5–71.8	48.5–71.8
	N (%)	N (%)	N (%)	N (%)	N (%)
Male/female	42/5	41/5	13/2	12/3	25/5
Stage					
III	4 (8.5)	4 (8.7)	2 (13.3)	0	2 (6.7)
IV	43 (91.5)	42 (91.3)	13 (86.7)	15 (100)	28 (93.3)
Tumor site					
Oral cavity	5 (10.6)	4 (8.7)	1 (6.7)	2 (13.3)	3 (10.0)
Oropharynx	24 (51.1)	24 (52.2)	8 (53.3)	8 (53.3)	16 (53.3)
Hypopharynx	12 (25.5)	12 (26.1)	4 (26.7)	2 (13.3)	6 (20.0)
Larynx	4 (8.5)	4 (8.7)	1 (6.7)	3 (20.0)	4 (13.3)
Unknown primary	2 (4.3)	2 (4.3)	1 (6.7)	0	1 (3.3)
Reason for unresectability					
Tumor size	28 (59.6)	28 (60.9)	8 (53.3)	9 (60.0)	17 (56.7)
Tumor accessibility	2 (4.3)	2 (4.3)	1 (6.7)	0	1 (3.3)
Infiltration adjacent structure	13 (27.7)	12 (26.1)	4 (26.7)	5 (33.3)	9 (30.0)
Too mutilating	1 (2.1)	1 (2.2)	0	1 (6.7)	1 (3.3)
Other	3 (6.4)	3 (6.5)	2 (13.3)	0	2 (6.7)
Performance status					
0	30 (63.8)	29 (63)	9 (60.0)	10 (66.7)	19 (63.3)
1	17 (36.2)	17 (37)	6 (40.0)	5 (33.3)	11 (36.7)
Current smoker	30 (63.8)	29 (63)	7 (46.7)	9 (60.0)	16 (53.3)
History of alcohol abuse	28 (59.6)	27 (58.7)	8 (53.3)	7 (46.7)	15 (50.0)

Table 2. Chemoradiation treatment adherence

	Cisplatin arm		Carboplatin arm	
Radiation				
Duration (weeks)				
Median	7		7.1	
Range	3–8.1		6.7–8.1	
Cumulative dose (Gy)				
Median	70.0		70.0	
Range	20.4–70.0		69.8–70.0	
	Cisplatin	Cetuximab	Carboplatin	Cetuximab
	n (%)	n (%)	n (%)	n (%)
Systemic treatment				
Number of administrations				
0	0	0	0	1 (6.7)
1	0	0	0	0
2	1 (6.7)	0	0	1 (6.7)
3	1 (6.7)	1 (6.7)	1 (6.7)	1 (6.7)
4	1 (6.7)	1 (6.7)	2 (13.3)	0
5	4 (26.7)	1 (6.7)	1 (6.7)	1 (6.7)
6	2 (13.3)	2 (13.3)	0	2 (13.3)
7	6 (40.0)	9 (60.0)	8 (53.3)	5 (33.3)
8	0	1 (6.7)	3 (20.0)	3 (20.0)
11	0	0	0	1 (6.7)
Cumulative dose (range)				
Unit	mg/m ² /week	mg/m ² /week	mg/ml/min/week	mg/m ² /week
Median	34.8	238.1	1.5	243.2
Range	11.0; 40.1	148.1; 285.7	0.6; 1.5	0; 385.0

Table 3. Dose intensity during biochemoradiation

	Cisplatin arm	Carboplatin arm
Cisplatin		
Median	34.8	1.5
Range	11.0–40.1	0.6–1.5
Cetuximab		
Median	238.1	243.2
Range	148.1–285.7	0.0–385.0

Cisplatin and cetuximab: mg/m²/week; carboplatin: AUC/week.

toxicity. Radiation was stopped prematurely in two patients (13.3%) in the cisplatin arm. It was interrupted temporarily in 1 (6.7%) and 4 (26.6%) patients in the cisplatin and carboplatin arm, respectively. Grade ≥ 3 toxicity during biochemoradiation is summarized in the supplementary Table S3, available at *Annals of Oncology* online. One patient in the cisplatin arm most likely died as result of toxicity (general physical deterioration). One patient in the carboplatin arm died due to pharyngeal bleeding 9 months after the end of biochemoradiation.

Feasibility of the biochemoradiation regimen

Of the 30 patients exposed to biochemoradiation, only 7 patients in the cisplatin arm (46.7%) and 8 patients in the carboplatin arm (53.3%) met the feasibility criteria of 80% dose intensity.

Treatment activity

Efficacy data are summarized in the supplementary Table S4 and Figures S2 and S3, available at *Annals of Oncology* online.

Discussion

The primary endpoint of this randomized phase II study was to test the feasibility of biochemoradiation with cetuximab and either weekly cisplatin 40 mg/m² or weekly carboplatin AUC 1.5 mg/ml/min after prior induction chemotherapy with TPF-E in association with cetuximab, a regimen which is also not yet prospectively validated. The primary objective was to select the most feasible platinum strategy in biochemoradiation after TPF-E in a future phase III trial. A total of 47 patients entered the study (instead of the 55 planned) of whom ultimately 31 after induction could be randomized for chemoradiotherapy (instead of the 50 planned). The study was stopped prematurely because of safety issues encountered during the induction biochemotherapy phase and the higher than expected drop-out rate during this induction phase. Therefore, although only 47% and 53% of patients met the feasibility criteria of 80% dose intensity in the cisplatin and carboplatin arms, respectively, a definitive conclusion on the feasibility of the biochemoradiation part of the protocol could not be made due to the high number of drop-outs (33% of patients) before this part of the treatment.

Since the premature closing of our study, the combination of radiation, cisplatin, and cetuximab in patients with LA-HNSCC

has been abandoned after the publication of the results of RTOG protocol #0522, demonstrating that the addition of cetuximab to the radiation-cisplatin platform significantly increased toxicity and did neither improve PFS nor OS [9]. In our trial, biochemoradiation was preceded by cisplatin-based induction chemotherapy, an approach that although by itself demonstrated to be feasible in large randomized phase III trials, might increase toxicity of the subsequent platinum-based chemoradiation [10–14]. Biochemoradiation preceded by induction chemotherapy was attempted by Strojan et al. who planned to treat 30 patients with four cycles of TPF in patients with normal bone marrow, renal and hepatic function followed by RT in combination with weekly cetuximab and cisplatin, 30 mg/m², or carboplatin AUC 1.5 mg/ml/min (in case of creatinine clearance <60 ml/min and/or peripheral polyneuropathy grade >1). Only six patients (20%) were able to complete treatment (induction and concomitant part) according to the study protocol, without interruptions and chemotherapy substitutions [15].

Our study was closed early because of serious adverse events observed during the induction part of the protocol. In particular, the rate of febrile neutropenia and infectious events was high and the gastrointestinal adverse events were common and strikingly severe, among which three bowel perforations. Serious toxicities, in particular mucositis, infectious complications and gastrointestinal toxicities, including bleedings, have been encountered also with the American TPF regimen when given in full dose in combination with cetuximab (13). The American TPF regimen (cisplatin 100 mg/m² and docetaxel 75 mg/m², both on day 1, followed by 5-FU 1000 mg/m²/day, as a continuous infusion over 4 days) needed to be adapted when cetuximab was added. The maximum tolerated 5-FU dose in that TPF-E regimen was determined at 850 mg/m² [16]. DeLOS-II, a German multicenter randomized phase II trial in which the European TPF regimen (the regimen as used in our study) ± cetuximab was followed by RT (69.6 Gy) with or without cetuximab in patients with resectable laryngeal and hypopharyngeal cancer, also identified 5-FU as a critical drug in the combination with regards to toxicity. Cetuximab increased particularly the non-hematologic toxicity when combined with TPF/TP versus TPF/TP alone, and very often required dose reductions in both arms [17].

Experience in Spain, again with the European TPF plus cetuximab in a similar population as in our study (50 patients, all with unresectable disease), and using prophylactic antibiotics and G-CSF support from the start, is also in line with our conclusion, i.e. that full dose TPF plus cetuximab is unacceptably toxic. They encountered grade 3/4 neutropenia in 24%, febrile neutropenia in 20%, diarrhea in 12%, infections, thrombocytopenia and hepatotoxicity (all in 4%) and hypomagnesemia in 2% with two treatment related deaths [18].

The combination of cetuximab with a platinum/taxane doublet might be better feasible, although also here the addition of cetuximab led to reduced chemotherapy doses in several trials [19–23].

Moreover, the platinum/taxane doublets have not been compared with TPF, which is supported by multiple randomized phase III trials and by an individual patient based meta-analysis and which is therefore widely considered the induction chemotherapy regimen of choice.

We conclude that in our study the addition of cetuximab to full dose TPF induction chemotherapy in patients with

unresectable locoregionally advanced HNSCC led to unacceptable complications and premature closing of the study. Because of the high drop-out during the induction part, no definitive conclusions can be drawn about the feasibility of the biochemoradiation part of the treatment protocol. The feasibility of that part is however highly questionable, as only half of the patients received the pre-defined 80% dose intensity level in the biochemoradiation phase. Although the addition of cetuximab to chemoradiation with cisplatin does not improve outcome overall [9], there are indications that some subgroups still might benefit from this combination [24]. Therefore further study is needed. This accounts also for biochemotherapy; optimal partnership between chemotherapy and cetuximab should be looked for based on tolerance, safety and efficacy as well as a better selection of patients who might benefit from this approach.

We acknowledge several weaknesses in our trial including the use of weekly cisplatin or carboplatin which have not been validated as standard treatment regimens and the mixing of two questions, i.e. the addition of cetuximab to TPF induction chemotherapy and the addition of cetuximab to subsequent chemoradiation.

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