Outcome of patients with recurrent/metastatic squamous cell head and neck cancer treated with platinum-based chemotherapy with or without cetuximab in real-world practice

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Abstract. Patients with recurrent or metastatic squamous cell head and neck cancer (R/M SCHNC) exhibit a poor prognosis with a median overall survival (OS) time of <1 year. Platinum-based chemotherapy with or without cetuximab has been the standard of care in the last decade. The aim of the current retrospective study was to evaluate the outcome and tolerability of treatment in patients with R/M SCHNC receiving platinum/5-fluorouracil/cetuximab (PFE) chemotherapy compared with platinum/5-fluorouracil (PF) chemotherapy in daily clinical practice. A retrospective analysis was performed using the data of patients treated at the Institute of Oncology Ljubljana between April 2008 and May 2018. Progression-free survival (PFS) and OS were calculated with the Kaplan-Meier method and compared with the log-rank test. Multivariate regression Cox analysis was used to determine independent prognostic factors. A total of 67 patients were treated at the aforementioned Institute: 34 patients received the PF and 33 the PFE regimen. The mean age of patients was 54.6 years and 91% of patients were male. Median PFS time was 6.6 vs. 7.1 months for the PF vs. PFE groups, respectively (P=0.852). Median OS time was 9.6 vs. 11.5 months for the PF vs. PFE groups, respectively (P=0.029). The prognostic factor for PFS was partial remission [hazard ratio (HR), 0.32; 95% CI, 0.15-0.70; P=0.004]. Prognostic factors for OS were partial remission (HR, 0.15; 95% CI, 0.06-0.38; P<0.001) or stable disease (HR, 0.28; 95% CI, 0.13-0.64; P=0.002), and a subsequent line of treatment upon progression (HR, 0.28; 95% CI, 0.15-0.52; P<0.001). In the PFE group, 15.4% of patients had a grade >2 infusion reaction to cetuximab and 27.3% had grade 3 skin rash. There were no differences in diarrhoea, hypomagnesaemia, infections and febrile neutropenia; however, the mortality on active treatment was high (13.4%). In conclusion, patients treated with PFE had similar PFS, but improved OS compared with patients treated with the PF protocol. The proportion of patients who died under treatment due to disease progression and toxicity was high in both treatment arms. A thorough selection of patients for this treatment is crucial.

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Introduction

Head and neck cancer represents the seventh most common cancer in Slovenia and is more common in men than women. Squamous cell head and neck carcinoma (SCHNC) represents 90% of all head and neck cancer. The annual incidence is around 470 cases (1).

Despite multimodal treatment, 50 to 60% of stage III and IV cancers will relapse locoregionally and/or at distant sites. Surgical procedure and/or re-irradiation are therapeutical options, but rarely feasible. Patients could be treated with systemic therapy or best supportive care only. The decision depends on the patient's platinum-free interval, performance status (PS) and comorbidity (2).

In 2008, Vermorken *et al* reported the results of the phase III EXTREME trial, in which the addition of cetuximab to first-line platinum/5-fluorouracil chemotherapy (PFE regimen) significantly improved progression-free survival (PFS) and overall survival (OS) compared to platinum/5-fluorouracil (PE) only. The EXTREME regimen become the new standard of care for patients having very good PS (0-1) (3). Despite that, the prognosis of patients with recurrent and/or metastatic (R/M) SCHNC remains poor with a median OS of 10 months (4). In Slovenia, SCHNC survival rates are comparable to those in Western Europe (5).

In our country, the decision about the most suitable treatment for R/M SCHNC is made at the multidisciplinary tumour board at the Maxillofacial Department or the Head and Neck Surgical Clinic of two university clinical centres, Ljubljana, and Maribor, and at the Institute of Oncology Ljubljana. All patients referred for systemic therapy are treated at a single centre, at the Medical Oncology Department of the Institute of Oncology, Ljubljana.

We followed the international treatment guidelines (6), but the treatment with cetuximab was not fully reimbursed in the first years after European Medicine Agency (EMA) approval, and our patient population is also specific regarding the high percentage (20-25%) of grade 3 or 4 infusion reactions to cetuximab, which prevented our patients from receiving cetuximab (7). The primary aim of this retrospective study was to compare the outcomes of our patients with R/M SCHNC treated with the PF and PFE regimens in the routine clinical setting with outcome in a randomized trial and to identify possible prognostic factors for PFS and OS. The secondary aim was to assess the tolerability of the treatment.

Patients and methods

Study design. Patients with R/M SCHNC treated between April 2008 and May 2018 at the Institute of Oncology Ljubljana were included in this retrospective study. Data on patients and tumour characteristics and past treatments were retrieved from patients' charts. Patients gave written consent prior to treatment. The study protocol was reviewed and approved by the Institutional Ethics Committee (approval ID: ERIDNPVO: 0023-2020).

Patient selection. The selection of patients for this aggressive systemic treatment was performed at the multidisciplinary tumour board. Inclusion criteria for the PF and PFE protocols: First-line therapy for R/M SCHNC, PS 0-2, adequate haematologic, renal and liver function, approved reimbursement for cetuximab (for PFE only). Exclusion criteria for the PE and PFE protocols: Patients with nasopharyngeal carcinoma, PS >2. Exclusion criteria for PFE only: Infusion reaction to cetuximab grade >2 during the first cycle of cetuximab, prior treatment with cetuximab (patients who took part in the clinical study of concomitant radiation therapy plus cetuximab plus cisplatin), known allergy to bee or wasp venom grade >2, patients with bulky tumour in the oropharynx or larynx which would prevent urgent intubation in grade 4 cetuximab allergy. All patients who developed an allergy to cetuximab of grade >2 were treated with the PF protocol. Human papillomavirus (HPV) status in oropharyngeal tumours was not assessed in all patients and was not included in the analysis.

Treatment protocol. The PF regimen in both groups consisted of 5-fluorouracil (1000 mg/m^2 daily, 24-h continuous infusion) for 4 days and platinum-based chemotherapy [preferably cisplatin (100 mg/m^2, 3-h intravenous infusion), in case of neurological or kidney disfunction carboplatin AUC 5, -1-h infusion)] on day 2, every three weeks. In the PFE group, cetuximab was administered on the third day of the cycle at an initial dose of 400 mg/m^2 in a 2-h intravenous infusion (preceded by a test dose of 20 mg of cetuximab intravenously to test for an allergy), followed by weekly doses of 250 mg/m^2 in a 1-h intravenous infusion. Dose modifications of chemotherapy and cetuximab were permitted according to the drug-specified criteria. Granulocyte-stimulating growth factors were used based on clinician decision and standard recommendations.

Patients in both groups who achieved partial remission or at least stable disease received up to six cycles of chemotherapy. Patients in the PFE group who had at least stable disease after a maximum of six cycles of chemotherapy continued thereafter with cetuximab monotherapy every two weeks at a dose of 500 mg/m^2 until disease progression or unacceptable toxicity effects.

Patients in the PF group received no further active treatment and were followed-up regularly for disease progression.

Evaluation of therapy response. Response to the systemic therapy was evaluated clinically at every clinical visit before continuing with scheduled therapy. After the third or fourth cycle of therapy, computer tomography (CT) imaging of the involved regions was planned and obtained. Depending on the clinical situation, CT was obtained earlier. Response evaluation criteria in solid tumours (RECIST 1.1) were used (8). Assessment of adverse effects during therapy was according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (9). Infections, febrile neutropenia, skin rash, diarrhoea, and hypomagnesaemia were presented. Deaths during treatment were analyzed.

Statistical analysis. The characteristics of patients were categorically presented as frequencies and proportions. Age was presented as mean and range. Pearson chi-square test was used for statistical comparisons for categorical data and unpaired Student's t-test was used for comparing age between groups. In case of expected parameter values of <5 in >20% of cells, Fisher's exact test was used, which facilitates the analysis of smaller population sizes. A P-value ≤0.05 was considered statistically significant.

Treatment-free interval (TFI) was calculated from the date of finishing primary treatment [surgery or (chemo) radiotherapy] to the date of beginning of systemic treatment of relapsed disease. Platinum-resistant patients were those who progressed during the first 6 months after platinum-based treatment.

PFS was defined as the time from the date of the beginning of chemotherapy to the date of disease progression or death from any cause. OS was calculated from the date of the beginning of chemotherapy to the date of death from any cause.

Estimated survival rates and survival curves were generated by the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate regression analysis was performed in all patients (PF and PFE together) to assess the prognostic value of body mass index (BMI), type of systemic therapy (PF vs. PFE therapy regimen), response rate, and subsequent lines of chemotherapy. The prognostic significance was measured by hazard ratio (HR), which was calculated using the Cox regression model. All statistical analysis was performed using SPSS v.24.0 (IBM Corp.).

Results

Patients characteristics. Sixty-seven patients (61 male, 6 female) were included in the study. Exclusion criteria for cetuximab: 6 of 39 exposed to cetuximab (15.4%) had an allergy to cetuximab of grade >2, one had an allergy to bee or wasp venom, 2 had received prior cetuximab treatment,

Table I. Characteristics of patients treated with PF (n=34) and PFE (n=33).

Characteristics	PF	PFE	P-value
Mean age (range), years	54.7 (35-74)	54.4 (32-70)	0.88
Sex, n (%)			0.11[a]
Female	1 (2.9)	5 (15.2)	
Male	33 (97.1)	28 (84.8)	
Grade, n (%)			0.26
2	13 (38.2)	19 (57.6)	
3	6 (17.6)	5 (15.2)	
Unknown	15 (44.1)	9 (27.3)	
Location of primary tumour, n (%)			0.17[a]
Mouth	0 (0.0)	4 (12.1)	
Oropharynx	16 (47.1)	13 (39.4)	
Hypopharynx	10 (29.4)	9 (27.3)	
Larynx	5 (14.7)	7 (21.2)	
Paranasal sinus	1 (2.9)	0 (0.0)	
Other	2 (5.9)	0 (0.0)	
Primary stage, n (%)			0.05[a]
I	2 (5.9)	0 (0.0)	
II	3 (8.8)	0 (0.0)	
III	6 (17.6)	12 (36.4)	
IV	23 (67.6)	21 (63.6)	
Body mass index, n (%)			0.78[a]
<18.5	5 (14.7)	2 (6.1)	
18-24.9	23 (67.6)	24 (72.7)	
25-30	5 (14.7)	6 (18.2)	
>30	1 (2.9)	1 (3.0)	
Performance status, n (%)			0.15[a]
0	5 (14.7)	10 (30.3)	
1	28 (82.4)	22 (66.7)	
2	1 (2.9)	0 (0.0)	
3	0 (0.0)	1 (3.0)	
Primary treatment, n (%)			0.67[a]
Radiotherapy	3 (8.8)	2 (6.1)	
Surgery	4 (11.8)	3 (9.1)	
Chemoradiation	13 (38.2)	13 (39.4)	
Surgery and radiotherapy	5 (14.7)	4 (12.1)	
Surgery and chemoradiotherapy	8 (23.5)	6 (18.2)	
Chemotherapy	1 (2.9)	5 (15.2)	
Site of lesion at relapse, n (%)			0.44[a]
Local	19 (55.9)	12 (36.4)	
Regional	18 (52.9)	12 (36.4)	
Distant	15 (44.1)	17 (51.5)	
Primary metastatic	4 (11.8)	3 (9.1)	

[a]Fisher's exact test. PF, platinum/5-fluorouracil; PFE, platinum/5-fluorouracil/cetuximab.

2 refused cetuximab and 4 had an extensive oropharyngeal tumour with a difficult urgent intubation procedure. Finally, 34 patients were treated in the PF and 33 in the PFE group (Table I). One patient was African and all the others were Caucasian. The mean age was 54.6 years. Most patients were in PS 1 (82.4% of the PF group and 66.7% of the PFE group). The primary tumour was most often in the oropharynx (47.1% in the PE and 39.4% in the PFE group). In the PF group, half of patients relapsed locally and regionally, and 44% had distant metastases. In the PFE group,

Table II. Treatment characteristics of patients according to treatment with PF (n=34) and PFE (n=33).

Characteristics	PF, n (%)	PFE, n (%)	P-value
Number of chemotherapy cycles			0.93
1	4 (11.8)	2 (6.1)	
2	8 (23.5)	1 (3.0)	
3	6 (17.6)	8 (24.2)	
4	10 (29.4)	16 (48.5)	
5	3 (8.8)	5 (15.2)	
6	3 (8.8)	1 (3.0)	
Cetuximab cycles			NA
1-3	NA	2 (6.1)	
4-6	NA	4 (12.1)	
7-9	NA	3 (9.1)	
10-12	NA	4 (12.1)	
13-15	NA	7 (21.2)	
>15	NA	14 (42.4)	
Platinum component			0.79[a]
Cisplatin only	23 (67.6)	25 (75.8)	
Carboplatin only	4 (11.8)	2 (6.1)	
Cisplatin and carboplatin	7 (20.6)	6 (18.2)	
Response			0.17
CR	1 (2.9)	0 (0.0)	
PR	10 (29.4)	19 (57.5)	
SD	9 (26.5)	5 (15.2)	
Disease control (CR+PR+SD)	20 (58.8)	24 (72.7)	
PD	9 (26.5)	7 (21.2)	
Not evaluated	5 (14.7)	2 (6.1)	
Post-progression therapy			0.71
2nd-line treatment	8 (23.5)	6 (18.2)	
3rd-line treatment	7 (20.6)	13 (39.4)	

[a]Fisher's exact test. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PF, platinum/5-fluorouracil; PFE, platinum/5-fluorouracil/cetuximab; NA, not applicable.

one third of patients relapsed locally and regionally, and half had distant metastases. Of all patients, 7 patients were primary metastatic. The groups were balanced according to age, gender, body mass index (BMI), PS, tumour grade and primary site of progression (Table I). Median treatment free interval (TFI) in 60 patients (primary metastatic excluded) was 18 months (95% CI: 4.0-52.0). Of them, 4 patients were platinum resistant (one in PS 0, others in PS 1). All 4 were treated with the PF protocol.

Treatment characteristics. The treatment characteristics of both groups are presented in Table II. The median number of chemotherapy cycles for both groups was 4. Regarding the platinum component, only 11.8% of the PF and 6.1% of the PFE group were treated with carboplatin; all others received cisplatin at least in one cycle. Cisplatin was used in all cycles in 67.7% of the PF and 75.8% of the PFE group. Disease control was achieved in 58.8% of the PF and 72.7% of the PFE group. There were numerically more partial responses in the PFE group and more stable disease in the PF group, but the difference did not reach statistical significance (P=0.17). Post-progression systemic treatment was performed in 44% of patients in the PF and in 58% in the PFE group.

PFS and OS. Median follow-up time was 30.7 months. Median PFS for all patients was 6.6 months (95% CI: 5.0-8.3); median PFS was 7.1 months (95% CI: 4.6-9.6) and 6.6 (95% CI: 4.2-9.1) for the PFE vs. the PF group, respectively. There was no statistical difference in median PFS between groups (P=0.852; Fig. 1). Median OS for all patients was 10.2 months (95% CI: 9.3-11.1). In the PFE group, OS was 11.5 months (95% CI: 8.1-14.9), and in the PF group 9.6 months (95% CI: 7.4-11.8) and was clinically importantly longer (for 1.9 months) and statistically significant (P=0.029; Fig. 2).

Prognostic factors. Possible prognostic factors for PFS and OS are presented in Tables III and IV, respectively. For PFS, the only independent prognostic factor was partial response to treatment. For OS, in addition to the response rate, the

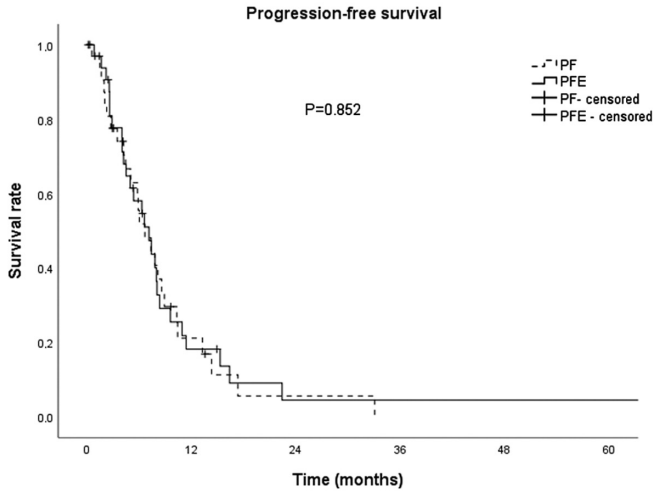

Figure 1. Progression-free survival curves for PF and PFE regimens. Median PFS time for the PF group was 6.6 months, while that for the PFE group was 7.1 months (P=0.852). PF, platinum/5-fluorouracil; PFE, platinum/5-fluorouracil/cetuximab.

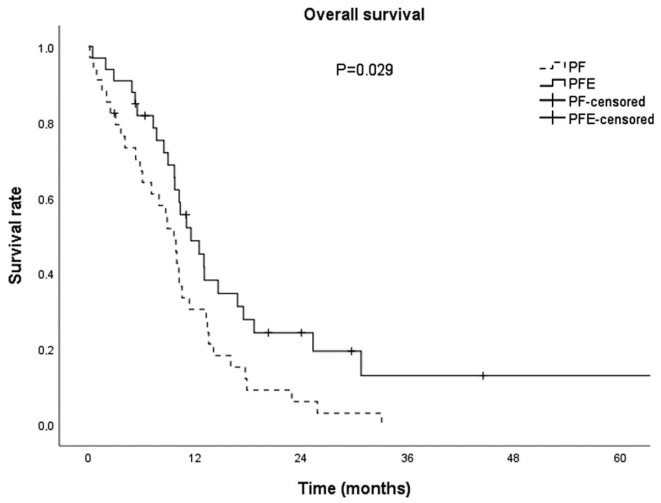

Figure 2. Overall survival curves for PF and PFE regimens. Median OS time for the PF group was 9.6 months, while that for the PFE group was 11.5 months (P=0.029). PF, platinum/5-fluorouracil; PFE, platinum/5-fluorouracil/cetuximab.

number of treatment lines (more than 1) was statistically significant. BMI >25 was also nearly statistically significant.

Tolerability of treatment. The tolerability of treatment is presented in Table V. During treatment with the PF and PFE protocols, hypomagnesaemia occurred in 44.6 and 57.6% of patients, respectively. Only one patient had grade 3 hypomagnesaemia (in the PFE group), all others were of grade 1 or 2. Skin rash of grade 1-3 was present in 85% of patients in the PFE group. Of them, 27.3% had grade 3 skin rash. Diarrhoea was a rare event; it was of grade 1 or 2 in 8.8% in the PF group and 6% in the PFE group. Infections (skin, malignant wound infection, bladder infection, oral mucositis, liver abscess, flu or pneumonia) were present in 41.2% of patients in the PF group and 33.3% in the PFE group. In both groups, one patient suffered febrile neutropenia. During treatment, 5 (14.7%) patients in the PF and 4 (12.1%) in the PFE group died due to adverse effects: Infection, bleeding, or sudden cardiac event.

Discussion

In this retrospective study, we presented the outcome and tolerability of the PFE and PE regimens in Slovenian patients with R/M SCHNC treated in the routine clinical setting. In a period of 10 years, half of the patients were treated in each group. OS in the PFE group was 11.5 months and was 1.9 months longer than in the PF group, which is statistically significant and clinically important. PFS did not differ between the groups. A high death rate due to disease progression and toxicity of treatment were the main issues. Hypomagnesaemia and skin rash were manageable with symptomatic measures.

In 2008, in the EXTREME study, OS of patients in the PFE regimen arm significantly improved from 7.4 to 10.1 months and PFS from 3.3 to 5.6 months, compared to those in the PF group. A higher response rate (36 vs. 20%) and a significant reduction of pain, and eating problems, and an improvement in speech were also reported (3). Our retrospective study showed a similar OS as the EXTREME study (11.5 months); however, the benefit of median OS for PFE vs. PF regimen was slightly smaller (1.9 months, compared to 2.7 months in the EXTREME study). This clinically lower benefit could be due to post-progression treatment in the PF group. Median PFS for PFE vs. PF was not statistically significant in our report. Regarding median PFS and OS with platinum-based chemotherapy and cetuximab, similar results to ours were reported by other real-world studies (10-14).

Due to poor prognosis of R/M HNSCC, data on possible prognostic factors affecting OS and PFS are of great clinical value (10-14). In our study, favourable prognostic factors for OS were achieving an objective response to therapy and receiving a subsequent line of treatment after progression upon first-line treatment. OS tends to be longer in slightly overweight patients (BMI >25). The only prognostic factor for PFS was response rate (achieving partial remission).

Depenni *et al* (10) found independent unfavourable prognostic factors for OS and PFS in PFE regimen PS >0, presence of residual tumour at the primary site, platinum resistance and lack of objective response. Magnes *et al* (11) reported PS >1, leucocytosis and increased C-reactive protein, treatment-free interval <12 months and less intensive chemotherapy as prognostic factors for OS. Similarly to our results, in a Japanese population, patients with response to therapy (i.e. receiving ≥4 cycles of chemotherapy) had a better prognosis for OS (12). Response to systemic therapy is the major factor that affects survival in R/M SCHNC (15,16). However, according to Anderson *et al*, it is generally difficult to distinguish between cases where response affects survival and cases where response identifies patients with pre-treatment characteristics that favour longer survival (17). Nevertheless, our data and data in a Japanese population (12) show that patients able to receive more lines of systemic therapy live longer.

Up to 57% of patients with SCHNC present with malnutrition, with more than 10% weight loss from baseline body mass. BMI has been found to be a useful tool to evaluate nutritional

Table III. Univariate and multivariate analyses for prognostic factors regarding progression-free survival.

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Body mass index				
<25	1.00			
≥25	0.73 (0.37-1.44)	0.73	NA	NA
Cetuximab				
No	1.00			
Yes	0.95 (0.55-1.63)	0.85	NA	NA
Response rate				
Progressive disease	1.00		1.00	
Complete response	0.34 (0.04-2.60)	0.30	0.43 (0.05-3.50)	0.43
Partial response	0.26 (0.13-0.52)	<0.01	0.32 (0.15-0.70)	<0.01
Stable disease	0.59 (0.27-1.28)	0.18	0.57 (0.26-1.24)	0.16

HR, hazard ratio; NA, not applicable.

Table IV. Univariate and multivariate analyses for prognostic factors regarding overall survival.

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Body mass index				
<25	1.00		1.00	
≥25	0.44 (0.21-0.94)	0.035	0.46 (0.21-1.029	0.057
Cetuximab				
No	1.00		1.00	
Yes	0.56 (0.33-0.94)	0.029	0.82 (0.46-1.45)	0.494
Response rate				
Progressive disease	1.00		1.00	
Complete response	0.46 (0.06-3.53)	0.462	0.26 (0.03-2.22)	0.224
Partial response	0.13 (0.06-0.28)	<0.001	0.15 (0.06-0.38)	<0.001
Stable disease	0.30 (0.14-0.64)	0.002	0.28 (0.13-0.64)	0.002
Subsequent chemotherapy				
1	1.00		1.00	
>1	0.39 (0.23-0.66)	0.001	0.28 (0.15-0.52)	<0.001

HR, hazard ratio.

status that should be routinely assessed before treatment plans in SCHNC (18). The association between BMI and survival is not consistent across cancer types, stages and even sex, but in some cancer types BMI >25 was associated with favourable OS (19). Having BMI >25 tends to carry a beneficial prognosis for OS in our study. Similar to our results, a Canadian observational study revealed that BMI >25 at diagnosis is associated with improved survival; additionally, in their study, BMI <19 was associated with decreased OS (20).

In our analysis, cetuximab treatment was not an independent prognostic factor for OS. However, our study was not randomized, but findings were similar to the randomized EXTREME study, where patients with Karnofsky score <80 did not benefit from the addition of cetuximab to chemotherapy (3). This indicates that PFE should be preferred for patients in PS 0. Less intensive chemotherapies combined with cetuximab also led to improved OS and represent options for second-line treatment (21,22). Fragile patients might be more susceptible to toxicity due to local and systemic inflammatory responses triggered by cetuximab-induced antibody-dependent cellular cytotoxicity (11).

The EXTREME regimen has considerable toxicity and the logistics of managing three concomitant drugs. 5-fluorouracil requires 24-h continuous infusion for 4 days and is associated

Table V. Analysis of adverse effects during treatment with PF (n=34) and PFE (n=33).

Adverse effect	PF, n (%)	PFE, n (%)	P-value
Hypomagnesaemia			0.60[a]
Grade 1	12 (35.3)	15 (45.5)	
Grade 2	3 (8.8)	3 (9.1)	
Grade 3	0 (0)	1 (3.0)	
Grade 4	0 (0)	0 (0)	
Skin rash			<0.01[a]
Grade 1	NA	10 (30.4)	
Grade 2	NA	9 (27.3)	
Grade 3	NA	9 (27.3)	
Grade 4	NA	0 (0)	
Diarrhoea			0.50[a]
Grade 1	2 (5.9)	0 (0)	
Grade 2	1 (2.9)	2 (6)	
Grade 3	0 (0)	0 (0)	
Grade 4	0 (0)	0 (0)	
Infections	14 (41.2)	11 (33.3)	>0.99[a]
G1	Unknown	Unknown	
G2	4 (11.8)	9 (27.3)	
G3	7 (20.6)	1 (3.0)	
G4	0 (0)	0 (0.0)	
G5	3 (8.8)	1 (3.0)	
Febrile neutropenia	1 (2.9)	1 (3.0)	1.00
Death during treatment	5 (14.7)	4 (12.1)	>0.99
Causes of death			
Exsanguination	2 (5.9)	2 (6)	
Sudden cardiac death	1 (2.9)	1 (3)	
Pneumonia	1 (2.9)	1 (3)	
Abscess	1 (2.9)	0 (0)	

[a]Fisher's exact test; PF, platinum/5-fluorouracil; PFE, platinum/5-fluorouracil/cetuximab; NA, not applicable.

with an increased rate of mucositis, diarrhoea and cardiac events (11). Cisplatin needs optimal antiemetic treatment and close observation of renal function, high hydration and magnesium supplementation. Cetuximab causes infusion reaction, skin toxicity and hypomagnesaemia.

In our retrospective analysis, we found several issues that should be discussed. Firstly, 15.4% of our patients exposed to cetuximab had a grade 3 or 4 infusion reaction. This is considerably higher than in the EXTREME study. We reported a similar rate in our previous study (7). Secondly, the incidence of a grade 3 skin reaction (Table V) was also high: 27.3% in comparison to 9% in the EXTREME study. These patients needed intensive supportive care. Hypomagnesaemia was predominantly of grade 1 or 2, but we performed very stringent preventive measures for hypomagnesaemia. Diarrhoea (a side effect of 5-fluorouracil) was not clinically important; <10% of patients had grade 1 or 2 diarrhoea. A very important fact is that 41.2% in the PF group and 33.3% in the PFE group had infections. We suppose that the high rate of infections in both groups could be due to the high percentage of locoregional or regional relapse (over 50% in PF and over 36% in PFE), which could cause tumour wound infections and also aspiration pneumonia due to difficulties in swallowing. The incidence of febrile neutropenia was low (2-3%). A very important message from our study is reflected in the number of deaths possibly related to treatment: 5 deaths (14.7% of patients) in the PF group and 4 deaths (12.1% of patients) in the PFE group. The causes are presented in Table V: Infections, bleeding and sudden cardiac events.

In the EXTREME protocol, there were 10 (2.3%) treatment-related deaths among 434 patients and an additional 4 (0.9%) cases of death due to sudden cardiac death. Despite these complications and the small number of patients, OS of our patients is better than real-world global OS, which is reported at 8.0 months (14). This is probably due to the appropriate selection of patients for systemic therapy in our daily practice. In a real-world population (14), one third of patients were platinum resistant, which carries poor prognosis (10,11,14). In our study, 4 (6%) patients were platinum resistant and died within three months of therapy.

Because of the small number of patients, we cannot conclude which regimen carries higher mortality and more adverse effects. According to the ENCORE study, only 5% of serious adverse events could be attributed to cetuximab (13).

Limitations of the study. The main limitations of our study are the small number of patients and retrospective data collection. Many patients were not treated with cetuximab due to limited access to the drug (no reimbursement) or were unable to tolerate it (a substantial rate of grade 3/4 infusion reactions). Finally, HPV status was not assessed and its prognostic impact could not be evaluated.

The main advantage of this study is that all patients were treated at a single comprehensive oncological centre with specialist medical personnel (medical oncologists, specialist nurses and nutritional therapists), which assured an optimal treatment regimen and side effects management. In our real-world practice, patients were treated with cisplatin as the preferred agent at the same dose and in a comparable percentage as in the EXTREME study. Our real-world treatment results will guide us to further improve the selection of patients appropriate for this aggressive treatment with short OS prolongation.

Recently, immunotherapy has become the new standard of care, especially for patients with inflamed tumour (23,24). The EMA has endorsed pembrolizumab as monotherapy or in combination with PF chemotherapy in the first-line treatment of R/M SCHNC in adults, based on programmed death-ligand 1 (PD-L1) expression for those with combined positive score >1 and PS 0 or 1 (25). It has been estimated that around 70-80% of patients with R/M SCHNC will be considered as eligible (24). On the other side, the PFE regimen still represents the optimal first-line therapy for the remaining 20-30% of fit patients with PD-L1 negative R/M SCHNC or patients contraindicated for anti-PD-L1 checkpoint inhibitors and as second-line treatment after progression on PD-L1 checkpoint inhibitors.

The analysis of patients with R/M HNSCC treated in Slovenia in the 10-year period revealed that patients treated with the PFE regimen have improved OS but not PFS when

compared to the PF regimen. Patients in either treatment group with objective response to therapy, in good nutritional status and suitable for further treatment at progression have a better prognosis. The proportion of patients who died under treatment due to disease progression and toxicity was high in both treatment arms. In everyday clinical practice, the thorough selection of patients and treatment at an experienced medical oncology centre is crucial.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TZ analyzed and interpreted the data and drafted the manuscript. BZ conceived and designed the study, analyzed and interpreted the data and critically revised the manuscript for important intellectual content. CGK conceived and designed the study, acquired the data, analyzed and interpreted the data, drafted the manuscript and critically revised the manuscript for important intellectual content. TZ and CGK are responsible for confirming the authenticity of the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Commission at the Institute of Oncology Ljubljana (Ljubljana, Slovenia). All procedures followed in this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Declaration of Helsinki of 1975, as revised in 2000. Individual patient consent was not collected for the present study as this was a retrospective database analysis, and the institutional informed consent form for treatment included consent to use the patients data, materials and/or test results for research purposes.

Patient consent for publication

Not applicable.

Competing interests

CGK presented these results at a meeting of Slovenian and Croatian head and neck cancer specialists held in Zagreb (Croatia) in December 2018 that was organised and sponsored by Merck, although Merck had no influence on the presentation of the results. TZ and BZ declare that they have no competing interests.

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