The EXTREME regimen for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): Treatment outcome in a single institution cohort

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Treatment of patients with locally recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) is a great challenge. The phase III EXTREME trial demonstrated that the addition of cetuximab to the combination platinum-based chemotherapy and 5-fluorouracil (5-FU) significantly prolonged median survival from 7.4 months to 10.1 months in patients with R/M HNSCC [1]. The purpose of this study was to evaluate the efficacy and toxicity of the EXTREME regimen in patients outside clinical trial.

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Methods

From October 2009 to March 2012, 22 consecutive patients with R/M HNSCC received the EXTREME-regimen at Rigshospitalet, University of Copenhagen, Denmark. The patients were recruited from 63 patients in need of palliative chemotherapy for R/M HNSCC. Their original primary tumors were localized in the oral cavity, parotid glands, larynx, or naso-, oro-, or hypopharynx. All patients had histologically confirmed recurrence or metastasis, and neither surgery nor irradiation was possible. The original biopsies from all patients were analyzed for HPV-status by p16 immunostaining. Only patients with WHO performance status (PS) 0–1 were included. The patients had acceptable hematopoietic, hepatic, and renal function. Patients were excluded if they had other active malignancy. One patient had known inactive prostate cancer. One patient received two cycles of the treatment as induction prior to brachytherapy and is therefore only included in the toxicity evaluation and not in the analysis of overall survival (see below).

The study was approved by the Danish Data Protection Agency.

Patients received a maximum of six cycles of cisplatin (at a dose of 100 mg/m^2) and cetuximab [at a dose of 400 mg/m^2 initially, as a 2-hour intravenous (loading dose) infusion, then 250 mg/m^2, as a 1-hour intravenous infusion per week] on day 1 and 5-FU (at a dose of 1000 mg/m^2 per day for 4 days) every three weeks followed by cetuximab maintenance with 250 mg/m^2 every week until disease progression, unacceptable toxicity, or death.

Tumor responses were assessed by CT or MRI at baseline and after three and six cycles of treatment and hereafter every third month for the patients who received weekly cetuximab until disease progression. Tumor response evaluation was done by Response Evaluation Criteria in solid tumors (RECIST) version 1.1 [2]. Adverse events were monitored according to Common Terminology Criteria for Adverse Events v. 4.0 2009 (CTCAE) [3]. Follow-up time was 48–732 days.

The endpoints were toxicity of the treatment, overall survival (OS), overall response rate (ORR), disease control rate (DCR) [= complete response (CR), partial response (PR), or stable disease (SD)] and progression-free survival (PFS). OS and PFS analyses were performed by the method of Kaplan-Meier [4].

Results

Patients' characteristics are seen in Table I.

Six patients of 21 achieved a PR and four patients had SD. No patients achieved CR. ORR was 29% (0 CR, 6 PR) and DCR was 48% (0 CR, 6 PR, 4 SD). The median duration of PFS was 5.8 months (95% CI 4.3–7.3 months) and the median OS was 7.3 months (95% CI 5.0–9.7 months) (Figure 1).

Ten patients had grade 3 or 4 events of hypokalemia, nine had neutropenia, seven had skin reactions, five had febrile neutropenia, five had thromboembolic complications, and two had anaphylactic reaction. Two patients died of febrile neutropenia after the first cycle of treatment. Grade 3 and 4 toxicities are detailed in Table II. Chemotherapy was discontinued due to adverse events in seven patients and four patients chose to end the treatment because of deterioration in quality of life.

Thirteen patients were p16 negative and eight patients were p16 positive on analysis of their initial tumor biopsies at diagnosis. The median survival for

Table I. Patient and tumor characteristics.

Variables	n	%
Gender		
Female	4	18
Male	18	82
Age		
Median age	52	
Range	42–64	
Performance		
0	13	59
1	9	41
2	0	0
Site of primary		
Nasopharynx	1	5
Oral cavity	4	18
Oropharynx	14	64
Hypopharynx	1	5
Larynx	1	5
Other (parotis)	1	5
TNM stage		
I	1	5
II	2	9
III	2	9
IVA	13	59
IVB	2	9
IVC	2	9
Previous treatment		
Surgery	3	14
Surgery + RT	3	14
Surgery + RT + chemotherapy	2	9
RT	10	45
RT+ chemotherapy	2	9
EXTREME first treatment	2	9
Previous chemotherapy for R/M disease		
EXTREME first line	17	77
EXTREME second line	5	23
Extent of disease		
Locoregional recurrence	10	45
Metastatic disease	12	55

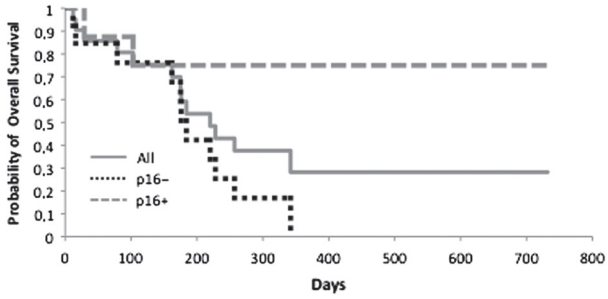

Figure 1. Overall survival of all patients and patients divided by p16 status.

p16 positive patients was not reached. The median survival for p16 negative patients was 6.1 months (Figure 1). Four of the five patients with grade 4 febrile neutropenia were p16 negative and four of the five patients with thromboembolic complications were p16 negative. Twelve patients had PS 0 and nine had PS 1. Seven of the of the eight p16 positive patients had PS 0 and one patient had PS 1, five of the p16 negative were PS 0 and eight were PS 1. As expected, the patients with PS 0 lived longer than the patients with PS 1.

Table II. Toxicity.

Variables	n	%
Patients	22	100
Anemia		
grade 3	4	18
grade 4	0	0
Allergic reaction		
grade 3	0	0
grade 4	2	9
Febrile neutropenia		
grade 3	0	0
grade 4	5	23
Hypokalemia		
grade 3	9	41
grade 4	1	4.5
total	10	45
Leukocytopenia		
grade 3	4	18
grade 4	3	14
total	7	32
Neutropenia		
grade 3	3	14
grade 4	5	23
total	8	36
Thrombocytopenia		
grade 3	1	4.5
grade 4	1	4.5
total	2	9
Thrombo-embolism		
grade 3	5	23
grade 4	0	0
Skin reaction		
grade 3	7	32

Discussion

This retrospective study of Danish patients treated for R/M HNSCC with the EXTREME regimen of cisplatin, 5-FU, and cetuximab demonstrates that the regimen is associated with severe side effects.

Two randomized phase III trials showed that patient with R/M HNSCC benefit with regard to survival by the addition of cetuximab to platinum-based chemotherapy. In 2005 Burtness et al. demonstrated in a study with 123 patients that cisplatin plus cetuximab gave a median survival of 9.2 months compared to 8.0 months in the control group with cisplatin plus placebo. These results, however, were not significant ($p = 0.21$) [5]. Vermorken et al. showed a significantly prolonged survival from 7.4 months in the control group receiving platinum-based chemotherapy and 5-FU to 10.1 months in the group that received the same chemotherapy plus cetuximab [4].

In this present study the median OS was 7.3 months (95% CI 5.0–9.7) which is not different from the former standard treatment with platinum-based monotherapy [1,5,6]. The median survival for patients whose original tumor was p16 positive was not reached, and the median survival for patients whose primary tumor was p16 negative was 6.1 months. This raises the question whether R/M HNSCC p16 negative and R/M HNSCC p16 positive patients benefit from and tolerate the same treatment. Our results indicate that p16 negative patients have a poorer prognosis than p16 positive patients also in the relapse setting. However, the results do not demonstrate whether the treatment is more efficient in p16 positive patients or whether the p16 positive patients are in better general condition, even at relapse, and thus better able to tolerate the relatively toxic regimen. In the present study 13 of the 21 patients were p16 negative and they had poorer general health and developed more severe side effects than the p16 positive patients.

Another explanation for the short median overall survival is that the EXTREME-regimen may be more toxic when used outside clinical trials. In the Vermorken et al. study 4% of the patients withdrew consent, and adverse events led to discontinuation in 20% of the patients in both the control group and the group treated with chemotherapy plus cetuximab [1]. In the current study, four of 22 patients chose to end the treatment due to negative impact on quality of life, and seven of 22 patients had to end the treatment because of severe adverse events. Hence 11 of 22 ended the treatment due to side effects. Three patients died within the first months due to side effects of the treatment. Two patients died of febrile neutropenia after the first cycle of treatment. Both patients were in good health apart from the

R/M HNSCC diagnosis, had PS 1, were physically active, and had no comorbidities. One patient developed pancytopenia after the first cycle of treatment and died 29 days later in a hospice. The patient had in 1989 undergone allogenic bone marrow transplantation and total body irradiation (TBI, 12 Gy) for acute myeloid leukemia and had been treated for relapse of the HNSCC five times with surgery, radiation (IMRT 66 Gy), brachytherapy, total laryngopharyngectomy with hyperbaric oxygen therapy, and nine cycles of paclitaxel and capecitabine without any sign of bone marrow suppression. The patient had PS 1 and was eager to try the EXTREME regimen when diagnosed with relapse for the sixth time. However, he had for months before been weakened due to a *Clostridium difficile* infection. Two patients developed grade 4 infusion-related anaphylactic reactions when treated with cetuximab, which match results found by Keating et al. in a retrospective study of 125 patients with various cancer types receiving cetuximab. They found that 14.5% experienced a grade 3 or 4 allergic reaction [7].

Twenty-three percent (5/22) of our patients developed grade 3 venous thromboembolic complications (VTEs) with deep vein thrombosis and pulmonary embolism. Cancer patients are known to have a four-fold higher risk of venous or arterial thromboembolism, and treatment with chemotherapy increases the risk [8]. Moore et al. found in a large retrospective analysis of 932 cancer patients with any type of malignancy receiving cisplatin-based treatment that 18.1% developed arterial or venous thromboembolic events. HNSCC patients are not normally considered high-risk cancer patients for developing thromboembolic events, but Moore et al. found that 12.8% (12/94) head and neck cancer patients developed arterial or venous thromboembolic complications [8].

In the EXTREME trial there is no report of any venous or arterial thromboembolic complications [9]. The consequences of thromboembolic events are serious, leading to long-term anticoagulation treatment with a bleeding risk, and, more importantly, increased mortality, as thrombotic events are the second leading cause of death of cancer patients (after cancer itself). Burtness et al. found that three of 58 patients developed VTEs and one patient had a VTE in the control group not receiving cetuximab. Modern targeted therapies, such as antiangiogenic agents and agents targeting vascular endothelial growth factor (VEGFR), are associated with an increased risk of developing venous or arterial thromboembolic complications. However, little is known about the risk of vascular events associated with EGFRs [10].

There are several limitations to this study. The follow-up time is 48–732 days, the study group consists of only 22 patients, and as mentioned above the group of patients was very heterogeneous. However, patients with recurrent or metastatic head and neck cancer are often heterogeneous. Our cohort included one patient with nasopharyngeal SCC, one patient with SCC of the parotid gland, two patients who had survived several recurrences, and two patients where the treatment was the first treatment for a HSCNN presenting with metastatic disease. Twelve patients had previously been treated for recurrences several years prior to the present relapse. However, they all had PS 0–1 before starting the treatment.

In conclusion, the current retrospective study indicates that the EXTREME-regimen may not add as much to overall median survival and may be more toxic than expected when used in patients with R/M HNSCC outside clinical trials. The results also suggests that R/M HNSCC patients whose original tumors were p16 positive may benefit more from the EXTREME-regimen than patients with p16 negative primary tumors. Effective regimens of cetuximab and chemotherapy with less toxicity for the palliative treatment of R/M HNSCC patients are highly desirable and relevant to investigate.

Declaration of interest: The authors report no conflicts of interest.

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