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Outcome of recurrent and metastatic head and neck squamous cell cancer patients after first line platinum and cetuximab therapy

Marco Siano [a,b,*], Gabriele Infante [c,d], Carlo Resteghini [a], Maria Chiara Cau [a], Salvatore Alfieri [a], Cristiana Bergamini [a], Roberta Granata [a], Rosalba Miceli [c], Laura Locati [a], Lisa Licitra [a,e], Paolo Bossi [a]

[a] Fondazione IRCCS Istituto Nazionale dei Tumori, Head and Neck Medical Oncology Dept., Via Venezian 1, I-20133 Milan, Italy
[b] Cantonal Hospital St. Gallen, Dept. of Med. Oncology and Hematology, Rorschacherstrasse 95, CH-9007 St. Gallen, Switzerland
[c] Fondazione IRCCS I.N.T., Clin. Epidemiology and Trials Org. Unit, I-20133 Milan, Italy
[d] Politecnic University Milan, Piazza Leonardo da Vinci, 32, I-20133 Milano, Italy
[e] State University of Milan, Via Festa del Perdono, 7, I-20122 Milano, Italy

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ABSTRACT

Objectives: Second-line chemotherapy in recurrent and/or metastatic head and neck cancer (r/mHNSCC) patients showed dismal results with limited tumor response and reduced life expectancy. Outside of clinical trials, data on efficacy of second line treatment after first line anti-EGFR-AB combination therapy are not available.

Material and methods: Data regarding r/mHNSCC consecutive pts treated with cetuximab and platinum from 2009 to 2014 at our center were retrospectively collected. The analyses of response, Progression-Free Survival (PFS) and Overall Survival (OS), each evaluated starting from first and second-line treatment, were performed. Survival curves were estimated with the Kaplan-Meier method and compared using the log-rank test.

Results: We identified 117 patients treated with first-line platinum and cetuximab-based therapy. Sixty-four (55%) patients did not receive second-line treatment due to worsening in performance status, 2 were not assessable for response thus 51 patients were included for analysis. Fifty-six percent were smokers/-former smokers and 78% were male. Primary tumor sites were oropharynx (39%), oral cavity (31%), larynx/hypopharynx (24%) and others (6%). Regimens used in second-line were mostly monotherapies. Twenty-one % of the patients were treated within a clinical trial.

Response rate (PR, CR) was 6% with 45% showing SD as best response. Median PFS was 2.2 months (95% CI:1.5–2.8 months) and OS 6.1 months (95%CI:3.7–7.2 months).

Conclusions: Within our single center experience only half of the patients with r/mHNSCC were able to receive second-line treatment. Response rate was unsatisfactory, but median OS seems higher than previously reported in an anti-EGFR-AB naïve population (Leon 2005).

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Introduction

Up to now, platinum containing combination chemotherapy (cisplatin or carboplatin) administered with the anti-epidermal growth factor receptor monoclonal antibody (anti-EGFR-AB) cetuximab is the only regimen able to prolong overall survival (OS) compared to chemotherapy alone in first-line r/mHNSCC [1]. In the trial, which lead to the approval of this combination, patients had a good performance status at inclusion (PS of 0–1) and median OS improved from 7.4 to 10.1 months (hazard ratio of cetuximab plus chemotherapy vs chemotherapy, 0.8; 95% CI, 0.64 to 0.99; P = 0.04). The trial, called EXTREME trial, was published in 2008 and shortly thereafter cetuximab was approved by the authorities and applied by the oncologic community.

In second-line, tyrosine kinase inhibitors (TKIs) gefitinib and afatinib (a pan-EGFR-TKI) have been investigated in phase III trials in comparison to mono-chemotherapy, without significant OS prolongation [2,3]. Novel checkpoint inhibitors, mostly anti-PD1 antibodies, are changing second-line treatment. FDA recently approved pembrolizumab and nivolumab in this setting, the latter based on a published randomized phase III trial showing a modest but

* Corresponding author at: Fondazione IRCCS Istituto Nazionale dei Tumori, Head and Neck Medical Oncology Dept., Via Venezian 1, I-20133 Milan, Italy and Cantonal Hospital St. Gallen, Dept. of Med. Oncology and Hematology, Rorschacherstrasse 95, CH-9007 St. Gallen, Switzerland.
E-mail address: marco.siano@kssg.ch (M. Siano).

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clinically meaningful OS benefit and improvement for quality of life parameter [4].

Studies reporting second-line treatment in r/mHNSCC are scarce, with the most frequently cited publication in this setting being the one by Leon et al. already published in 2005, before the cetuximab era [5]. After the adoption of standard anti-EGFR-AB combination treatment with chemotherapy in first-line setting, data about feasibility and activity of second-line chemotherapy are still not available.

Moreover, evidence regarding prognostic factors in this setting is also limited, since available data was generated for first-line treatment and within randomized trials not applying cetuximab [6].

We therefore retrospectively analyzed in our high-volume referral center all patients treated with standard first-line platinum and anti-EGFR-AB containing regimen, having a closer look to the ones receiving second-line therapy. The main objectives were to generate outcome data in a real-life setting for second line treatment in r/mHNSCC after progression on standard chemotherapy plus cetuximab therapy.

Patients and methods

Patients and data collection

All the clinical charts of the patients treated with cetuximab and platinum-based chemotherapy for r/mHNSCC in first-line setting at the National Cancer Institute of Milan between 2009 and 2014 were retrospectively analyzed and considered for final analysis. Most information was available through review of the electronical patient chart. Missing data were retrieved from the paper chart if necessary. If not available, date of death was retrieved from the residential municipality of the patients. We registered baseline patients characteristics, demographics and disease features including age at recurrent/metastatic disease, alcohol abuse, nicotine abuse in pack years (py), tumor site, HPV status by p16 and ISH (limited to oropharyngeal cancer), stage at primary diagnosis and at recurrence (according to the American Joint Committee on Cancer (AJCC) TNM staging system, 7th edition), ECOG performance status, previous treatment modalities, systemic treatment regimens and agents applied in each therapy line, cycles and duration of applied treatments, best response to first and second-line systemic treatments, and the dates of disease progression, death for any cause and last clinical follow up. Furthermore, we analyzed established prognostic factors previously validated before by Argiris et al. [6], in adjunct to HPV status and best response to first line treatment. The Ethical Committee of the National Cancer Institute of Milan approved the study.

Statistical analysis

Study end-points were the response rate, Progression-Free Survival (PFS) and Overall Survival (OS). Each end-point was evaluated from both the starting date of first-line treatment (when analyzing the population in all treatment lines), and second-line treatment (restricting to the subset of second line patients). The response rate was calculated as the percentage of pts with complete or partial response in respect to the total number of evaluable patients, and its 95% confidence interval was determined with the exact method. PFS was defined as the time from treatment start to clinically or radiologically confirmed disease progression or death; time was censored to the date of last follow-up for patients alive without progression. OS was defined as time from treatment start to death for any cause; time was censored to the date of last contact for patients alive. PFS and OS curves were estimated with the Kaplan-Meier method and compared using the log-rank test. We used a significance level of 5% for all the statistical tests. Statistical analyses were performed with SAS™ (9.04 version, copyright © 2012–2016, SAS Institute, Cary, NC) and R software (3.2.2 version, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2016).

Results

Patient characteristics

We identified 117 patients treated for r/mHNSCC with first-line platinum and cetuximab-based systemic therapy at our center. Patient demographics and characteristics are shown in Table 1.

Sixty-four patients (55%) did not receive second-line treatment due to worsening in performance status and 2 patients were not assessable for response. Therefore, 51 patients were included for analysis of second-line treatment, with most represented primary site being oropharyngeal cancer (39%), followed by oral cavity (31%), larynx/hypopharynx (24%) and other subsites in 6% of pts. Fifty-six percent were smokers/former smokers and 78% were male. HPV status was available in 16 oropharynx cancer pts with 6 being positive to p16 and HPV ISH analysis.

Systemic treatments applied

The distribution of first-line systemic treatments and respective combinations are shown in Table 2. In first-line, 26% of patients received a combination of 3-drugs with the addition of either 5-fluorouracil or paclitaxel.

Methotrexate was the most commonly administered agent in second-line; as academic cancer center devoted to cancer research,

Table 1
Pts. demographics and baseline characteristics (n = 117).

	n (%)
Median age	64
Range	(37–82)
Gender	
Male	86 (74)
Female	31 (26)
ECOG PFS	
0	31 (26)
1	69 (59)
>2	15 (13)
Not available	2 (2)
Smoking status	
Non-smoker	48 (41)
Smoker	62 (53)
Not available	7 (6)
≤20 py	4 (6)
>20 py	47 (76)
Not available	11 (18)
Prior local radiotherapy	
Yes	90 (77)
No	13 (11)
Not available	14 (12)
Primary tumor site	
Oropharynx	38 (32)
HPV pos. by ISH	9 (24)
Hypopharynx	4 (3)
Larynx	24 (21)
Oral Cavity	41 (35)
Other (Skin, CUP)	10 (9)
Stage at recurrence	
Locally advanced	45 (38)
Metastatic	46 (39)
Not available	26 (23)

CUP: Cancer of unknown primary. HPV: Human papilloma virus. ISH: In-situ hybridization.

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