Cent. Eur. J. Med. • 9(2) • 2014 • 279-284
DOI: 10.2478/s11536-013-0154-9

VERSITA

Central European Journal of **Medicine**

Cetuximab/cisplatin and radiotherapy in HNSCC: is there a favorite choice?

Rapid Communication

Jacopo Giuliani*[1], Marina Marzola[2]

1 Palliative Care Unit, Mater Salutis Hospital, ULSS 21, Legnago Verona, Italy

2 Clinical Oncology Unit - St. Anna University-Hospital, Ferrara Italy

Received 20 November 2012; Accepted 5 February 2013

Abstract: Introduction. In the absence of a published head-to-head trial between concomitant cisplatin-radiotherapy vs cetuximab-radiotherapy, we compared results of cetuximab vs cisplatin in unresectable HNSCC in our daily clinical practice. Materials and methods. We retrospectively analyzed all consecutive patients with unresectable HNSCC treated at Clinical Oncology Unit of the University Hospital of Ferrara (Italy) from October 2008 to February 2010. Results. We evaluated 21 patients: at last follow-up, 6 patients (28.6%) were deceased, 15 patients (71.4%) were alive and, among these, 13 (61.9%) were alive without evidence of disease (NED). Median follow-up time was 9.74 months. Median OS was 10.95 months. General characteristics were similar in the two subgroups, except for median age (low in cisplatin-subgroup: 55 vs 72) and the type of response (with a high numbers of complete response in cisplatin-subgroup). By the univariate analysis there was no statistical significance difference in OS (p= 0.898) between the two subgroups. Conclusions. Based on state-of-the-art, it was not possible to identify either treatment regimen is as superior in prolonging either locoregional control or OS: our results seem to indicate that the two treatments may be equally efficacious and deferring the choice of treatment on the toxicity profile. Head-to-head trials are needed.

Keywords: *Cetuximab • Head and neck cancer • Cisplatin • Concomitant radiotherapy*

© Versita Sp. z o.o

1. Introduction

Head and neck squamous cell carcinomas (HNSCC) accounts for 8% of newly diagnosed cancers in adults in worldwide [1]. A multidisciplinary treatment schedule should be established in all cases and treatment depends on primary tumor location and extension. Standard options for locally advanced stage III and IV tumors are surgery plus post-operative radiotherapy and, for those patients found at surgery to have high risk features (extracapsular extension and/or R1 resection), post-operative chemo–radiotherapy with single agent platinum [2-4]. Combined concomitant chemoradiation is the standard treatment in non-resectable patients or in resectable patients, when the anticipated functional outcome with surgery is poor [5]. Radiotherapy given concomitantly with cetuximab (Erbitux®, Merck-Serono, Darmstadt, Germany), a human-murine chimeric monoclonal antibody directed to the epidermal growth factor receptor (EGFR) binding site, has demonstrated a higher response rate, longer disease-free progression and longer overall survival versus radiotherapy alone [6]. In the absence of a published head-to-head trial between concomitant cisplatin-radiotherapy vs cetuximab-radiotherapy, we compared results of cetuximab vs cisplatin in unresectable HNSCC in our daily clinical practice; no studies like the above have been published until now.

2. Materials and methods

We retrospectively analyzed all consecutive patients with unresectable HNSCC treated at Clinical Oncology Unit of the University Hospital of Ferrara (Italy)

* *E-mail: giuliani.jacopo@alice.it*

Unauthenticated
Download Date | 9/19/19 2:35 AM

from October 2008 to February 2010; this period was selected in order to have two groups of patients balanced each others. All information was obtained from case history and reviewed the patient's medical history (from hospital records only). All data was registered in an Excel workbook. We excluded patients in which follow-up time was less than 1 month; follow-up time was defined as the time patients have been followed at our institution. Rare squamous head and neck cancer originating from paranasal sinuses and nasopharynx were excluded (they are usually excluded from trial treatment series supporting evidence-based recommendations). Also patients that were treated in clinical trials were not consider on our analysis. We divided the general case study into 2 subgroups: patients treated with concomitant cisplatin-radiotherapy and patients treated with concomitant cetuximab-radiotherapy and we compared clinical, pathological and therapeutical characteristic of both subgroups. A univariate analysis for overall survival (OS) was estimated according to the Kaplan-Meier method with statistical significance ($p<0.05$) of differences evaluated by log-rank test, censoring surviving patients at the last follow-up time. We chose to consider only OS and not progression free survival (PFS), because, in the absence of a prospective design to determine whether disease progression has occurred at specific defined intervals, this measurement is fraught with potential bias because patients may be followed with differing frequencies depending on whether or not they are in a clinical trial, or what specific therapy they are receiving.

3. Results

We evaluated 21 patients: at last follow-up, 6 patients (28.6%) were deceased, 15 patients (71.4%) were alive and, among these, 13 (61.9%) were alive without evidence of disease (NED). No patients were lost during follow-up (PFU). Median follow-up time was 9.74 months (range 3.06-20.03). Median OS was 10.95 months (range 2.73-20.82). Median age was 65 years (range 43-82). Twenty patients (95.2%) were male and 1 (4.8%) female; 17 patients (81.0%) were regular consumers of alcohol and all patients (100.0%) were smokers; regarding comorbidities, 10 patients (47.6%) had a cardiovascular disease, 2 patients (9.5%) arthrosis, 2 patients (9.5%) were major depressive, 1 patient (4.8%) a chronic obstructive pulmonary disease (COPD), 1 patient (4.8%) a LES and 5 patients (23.8%) had no comorbidities. The most frequent primary site was tonsil (38.1%). Stage IV was the most frequent (94.7%: 66.7% stage IVA, 14.3% stage IVB, 4.8% stage IVC); 2 patients (9.5%) had a local relapse. As of radiotherapy, mean dose was 68 Gy (range: 60-72 Gy) and median duration was 48 days (range: 19-86 days). Concomitant medical therapy was cetuximab for 9 patients (42.9%) and cisplatin for 12 patients (57.1%). Regarding the type of response, we have had in most cases a complete remission (CR), both for cT (71.4%) and cN (66.7%). The general case study is summarized on Table 1. Considering first subgroup (patients treated with concomitant cisplatin-radiotherapy), at last follow-up, 3 patients

Table 1. General case study.

Variable	Value	N° (%)	Variable	Value	N° (%)
Sex	Male	20 (95.2)	cN	cN0	2 (10.5)
	Female	1 (4.8)		cN1	2 (10.5)
Alcohol	Yes	17 (81.0)		cN2	13 (68.4)
	No	4 (19.0)		cN3	2 (10.5)
Smoking	Yes	21 (100.0)	Stage	III	1 (5.3)
Primitive site	Tonsil	8 (38.1)		IV	18 (94.7)
	Pyriform sinus	3 (14.3)	Concomitant schedule	Cisplatin	12 (57.1)
	Base of tongue	3 (14.3)		Cetuximab	9 (42.9)
	Hypopharynx	3 (14.3)	Type of response (cT)	CR	15 (71.4)
	Floor of the mouth	2 (9.4)		PR	2 (9.5)
	Soft palate	1 (4.8)		SD	1 (4.8)
	Larynx	1 (4.8)		PD	3 (14.3)
cT	cT1	1 (5.3)	Type of response (cN)	CR	14 (66.7)
	cT2	3 (15.8)		PR	3 (14.3)
	cT3	3 (15.8)		SD	1 (4.8)
	cT4	12 (63.2)		PD	3 (14.3)

Legend: N°= number of patients; CR= complete remission; PR= partial remission; SD= disease stabilization; PD= progression disease

Unauthenticated
Download Date | 9/19/19 2:35 AM

(25.0%) were deceased (in all cases for progression of disease) and 9 patients (75.0%) were NED. Median follow-up time was 8.00 months (range 3.49-20.03). Median OS was 8.55 months (range 2.73-20.82). Median age was 55 years (range 43-74). Eleven patients (91.7%) were male and 1 (8.3%) female. Stage IV was the most frequent (75.0%: 58.3% stage IVA, 8.3% stage IVB, 8.3% stage IVC) and 2 patients (16.0%) had a local relapse. Nine patients (75.0%) had received weekly cisplatin and 3 patients (25.0%) cisplatin each 21 days; considering weekly cisplatin, mean number of cycles was 5 (range: 1-7), instead considering cisplatin each 21 days, mean number of cycles was 2 (range: 1-3). As of radiotherapy, mean dose was 70 Gy (range: 62-72 Gy) and median duration was 44 days (range: 19-63 days). All patients (100.0%) were screened for nutritional assessment and all patients (100%) received nutritional support: in 5 patients (41.7%) a central venous catheter (CVC) was set and in 3 patients (25.0%) a percutaneous endoscopic gastrostomy (PEG) was set. Six patients (50.0%) were hospitalized for toxicities: 3 patients (50.0%) for severe neutropenia (grading 4) and 3 patients (50.0%) for mucositis (grading 3). Regarding the type of response, we have had in most cases a CR, both for cT (83.4%) and cN (75.1%). The case study of the first subgroup of patients is summarized on Table

Table 2. The concomitant cisplatin-radiotherapy patients case study

Variable	Value	N° (%)	Variable	Value	N° (%)
Sex	Male	11 (91.7)	cN	cN0	1 (10.0)
	Female	1 (8.3)		cN1	2 (20.0)
Alcohol	Yes	11 (91.7)		cN2	7 (70.0)
	No	1 (8.3)		cN3	0 (0.0)
Smoking	Yes	12 (100.0)	Stage	III	1 (10.0)
Primitive site	Tonsil	5 (41.7)		IV	9 (90.0)
	Pyriform sinus	2 (16.7)	Type of response (cT)	CR	10 (83.4)
	Base of tongue	2 (16.7)		PR	0 (0.0)
	Hypopharynx	1 (8.3)		SD	1 (8.3)
	Soft palate	1 (8.3)		PD	1 (8.3)
	Larynx	1 (8.3)	Type of response (cN)	CR	9 (75.1)
cT	cT1	1 (10.0)		PR	1 (8.3)
	cT2	2 (20.0)		SD	1 (8.3)
	cT3	1 (10.0)		PD	1 (8.3)
	cT4	6 (60.0)			

Legend: N°= number of patients; CR= complete remission; PR= partial remission; SD= disease stabilization; PD= progression disease.

Table 3. The concomitant cetuximab-radiotherapy patients case study

Variable	Value	N° (%)	Variable	Value	N° (%)
Sex	Male	9 (100.0)	cN	cN0	1 (11.1)
	Female	0 (0.0)		cN1	0 (0.0)
Alcohol	Yes	6 (66.7)		cN2	6 (66.7)
	No	3 (33.3)		cN3	2 (22.2)
Smoking	Yes	9 (100.0)	Stage	III	0 (0.0)
Primitive site	Tonsil	3 (33.4)		IV	9 (100.0)
	Pyriform sinus	1 (11.1)	Type of response (cT)	CR	5 (55.6)
	Base of tongue	1 (11.1)		PR	2 (22.2)
	Hypopharynx	2 (22.2)		SD	0 (0.0)
	Soft palate	2 (22.2)		PD	2 (22.2)
cT	cT2	1 (11.1)	Type of response (cN)	CR	5 (55.6)
	cT3	2 (22.2)		PR	2 (22.2)
	cT4	6 (66.7)		SD	0 (0.0)
				PD	2 (22.2)

Legend: N°= number of patients; CR= complete remission; PR= partial remission; SD= disease stabilization; PD= progression disease.

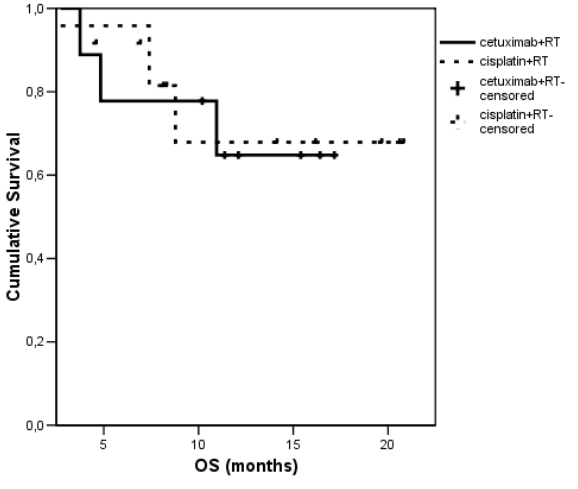
Unauthenticated
Download Date | 9/19/19 2:35 AM

2. Considering second subgroup (patients treated with concomitant cetuximab-radiotherapy), at last follow-up, 3 patients (33.3%) were deceased (in 33.3 of cases for progression of disease and in 66.7% for toxicities induced by treatment), 6 patients (66.7%) were alive and, among these, 4 (44.4%) were NED. Median follow-up time was 10.23 months (range 3.06-17.04). Median OS was 11.38 months (range 3.75-17.17). Median age was 72 years (range 64-82). All patients (100.0%) were male. All patients (100.0%) were stage IV (77.8% stage IVA and 22.2% stage IVB). Considering cetuximab, mean number of cycles was 7 (range; 4-9). As of radiotherapy, mean dose was 68 Gy (range: 60-70 Gy) and median duration was 53 days (range: 40-86 days). All patients (100.0%) were screened for nutritional assessment and 4 patients (44.4%) received nutritional support; in 3 patients (33.3%) a CVC was set and in 3 patients (33.3%) a PEG was set. Five patients (55.6%) were hospitalized for toxicities: 1 patient (20.0%) for severe neutropenia (grading 4) and 4 patients (80.0%) for mucositis (25.0% with grading 4). Regarding the type of response, we have had in most cases a CR, both for cT (55.6%) and cN (55.6%). The case study of the second subgroup of patients is summarized on Table 3. By the univariate analysis there was no statistical significance difference in OS (p= 0.898) between the two subgroups (Figure 1).

4. Discussion

In randomized, open-label, multinational, phase III clinical trials, cetuximab plus radiotherapy significantly improved the duration of locoregional control compared with radiotherapy alone in patients with locally advanced HNSCC [6]; in addition, cetuximab had an acceptable tolerability profile when added to radiotherapy and it did not exacerbate the toxicities commonly associated with these other treatment modalities, without an adverse impact on patients' health-related quality of life [7]. Therefore, cetuximab plus radiotherapy offers an alternative approach to the current standard of care (platinum-based chemotherapy plus radiotherapy) in the setting of locally advanced, unresectable disease. Referring to our experience, general characteristics were similar in the two subgroups (also with regard to the toxicities), with the exception for median age (low in first subgroup) and the type of response. Concerning median age, it is likely that the age higher in the second subgroup (72 vs 55) is linked precisely to the choice of cetuximab, which tends to be used in elderly people because of its favorable toxicity profile. Regarding the type of response we noticed a higher number of CR in first subgroup, but without any differencies at the univariate analysis for OS; however, a possible explanation could be that increasing the time of observation can also be seen future differences between the 2 two subgroups also in terms of survival. We also know both the limit of a retrospectve study, the small size of the cohorts and the fact that data coming from a single institution could reflect only the habits of that particular set of physicians; on the contrary, studies like the above, though the analysis of not selected casistics, are bale to evaluate treatment patterns in a real-world clinical practice, reflecting changes in therapy prescription. Moreover the current studies compare cetuximab plus radiotherapy, with the only radiotherapy and not with the combination platinum-radiotherapy, which represents the standard of care in this setting of patients [8,9]. To our knowledge only another study, remarking the absence of a published head-to-head trial, has estimated the relative benefit of cetuximab and cisplatin using an indirect comparison methodology: the authors agree with our conclusion, considering the two treatments may equally efficacious when given alongside radiotherapy and deferring the choice of treatment on the toxicity profile of the medications [10]. However, the main difference between the two types of studies is represented by the fact that in our experience we report data for direct comparison between cetuximab or cisplatin given concomitantly with radiotherapy into daily clinical practice. Instead, Levy AR et al [10] have performed a systematic review of the Medline and Embase databases between 1998 and 2008 to find published trials of cisplatin plus radiotherapy vs. radiotherapy alone and synthesized the information with meta-analysis and they combine those results with trial-based results of cetuximab plus radiotherapy vs.

Figure 1. Univariate analysis for OS considering concomitant cisplatin-radiotherapy vs concomitant cetuximab-radiotherapy patients.



Unauthenticated
Download Date | 9/19/19 2:35 AM

radiotherapy alone (is important to remark that this is a comparison with indirect methodology). In literature there are also reported experience with cetuximab plus platinum-based chemotherapy. In particular, some authors have investigated the efficacy of cetuximab plus platinum-based chemotherapy as first-line treatment in patients with recurrent or metastatic HNSCC: 220 of 442 eligible patients were randomly assigned to receive cisplatin or carboplatin plus fluorouracil every 3 weeks for a maximum of 6 cycles and 222 patients to receive the same chemotherapy plus cetuximab for a maximum of 6 cycles. Adding cetuximab to platinum-fluorouracil chemotherapy, significantly prolonged the median OS (from 7.4 to 10.1 months, hazard ratio for death= 0.80; p= 0.04), the median PFS (from 3.3 to 5.6 months, hazard ratio for progression= 0.54, p< 0.001) and increased the response rate (from 20% to 36%, p< 0.001) [11]. Other authors have experienced that single-agent cetuximab was active and generally well tolerated in the treatment of recurrent and/or metastatic HNSCC that progressed on platinum therapy and response was comparable to that seen with cetuximab plus platinum combination regimens in the same setting [12]. Even the combination of platinum and cetuximab with radiotherapy is also promising and may be better than any single chemotherapy combined radiotherapy [13]. Obviously identification of predictive biomarkers of resistance or sensitivity remains a crucial point in the optimal selection of patients most likely to benefit from targeted treatment: more studies are needed to maximize the efficacy of cetuximab in clinical settings and to identify the subpopulation of patients that truly benefit from its use [14]. In conclusion, we can consider cetuximab as an important therapeutical option in unresectable HNSCC. Based on state-of-the-art, it was not possible to identify either treatment regimen is as superior in prolonging either locoregional control or OS: actually the combination of platinum-radiotherapy is consider as the standard of care in this setting of patients. Head-to-head trials are needed.

5. Conflict of interest statement

None declared.

References

[1] Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60:277-300

[2] Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004;350:1937-1944

[3] Bernier J, Cooper JS. Chemoradiation after surgery for high-risk head and neck cancer patients: how strong is the evidence? Oncologist. 2005;10:215-224

[4] Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003;349:2091-2098

[5] Licitra L, Felip E; ESMO Guidelines Working Group. Squamous cell carcinoma of the head and neck: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009;20:121-122

[6] Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol. 2010;11:21-28

[7] Frampton JE. Cetuximab: a review of its use in squamous cell carcinoma of the head and neck. Drugs. 2010;70:1987-2010

[8] Forastiere AA. Chemotherapy in the treatment of locally advanced head and neck cancer. J Surg Oncol. 2008;97:701-707

[9] Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009;92:4-14

[10] Levy AR, Johnston KM, Sambrook J, et al. Indirect comparison of the efficacy of cetuximab and cisplatin in squamous cell carcinoma of the head and neck. Curr Med Res Opin 2011;27:2253-2259

[11] Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-1127

[12] Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol. 2007;25:2171-2177

Unauthenticated
Download Date | 9/19/19 2:35 AM

[13] Pfister DG, Su YB, Kraus DH, et al. Concurrent cetuximab, cisplatin, and concomitant boost radiotherapy for locoregionally advanced, squamous cell head and neck cancer: a pilot phase II study of a new combined-modality paradigm. J Clin Oncol 2006;24:1072-1078
[14] Kabolizadeh P, Kubicek GJ, Heron DE, Ferris RL, Gibson MK. The role of cetuximab in the management of head and neck cancers. Expert Opin Biol Ther 2012;12:517-528

Unauthenticated
Download Date | 9/19/19 2:35 AM