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ORIGINAL PAPER

Hypofractionated radiotherapy combined with cetuximab in vulnerable elderly patients with locally advanced head and neck squamous cell carcinoma

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Abstract
This study was designed to evaluate the objective response after hypofractionated radiotherapy (HFRT) combined with cetuximab (HFBRT) in vulnerable elderly patients with locally advanced head and neck squamous cell carcinoma (HNSCC). Vulnerable elderly patients with histologically proven HNSCC received HFRT (total dose 60 Gy, 3 Gy/fraction) with concurrent cetuximab (250 mg/m^2 with a loading dose of 400 mg/m^2 1 week before HFRT). Elderly patients were categorized as vulnerable based on mini-cog test and adult comorbidity evaluation-27 score. All patients completed the programmed HFRT and two patients received the planned cetuximab infusion. Severe acute toxicity, observed in four patients, was gastrointestinal (oral mucositis in four cases; nausea/vomiting in one case) and dermatological (acneiform eruption in three cases; radiation dermatitis in one case). Three serious adverse events were recorded in three out of six patients Overall, three patients had a partial response and three patients had progression disease 3 months after the end of the treatment. No complete response was observed. HFBRT seems to be not a safer alternative approach for vulnerable elderly patients with locally advanced HNSCC. Further prospective trials are needed to define better tumor control with less incidence of toxic effects in vulnerable elderly HNSCC patients.

Keywords Elderly · Older · Hypofractionated · Radiation therapy · Cetuximab · Head and neck · Squamous cell carcinoma

Introduction

Head and neck squamous cell carcinoma (HNSCC) requires a multidisciplinary management to improve clinical outcomes and manage treatment-related sequelae, such as xerostomia, speech and swallowing problems, neck lymphedema [1–4]. Based on the survival benefit in adding chemotherapy or cetuximab (bio) concomitantly to radiation therapy (RT), at present definitive cisplatin-based chemoradiotherapy (CRT) or bioradiotherapy (BRT) has become a care standard in HNSCC treatment [5, 6]. Over the past decade, the age of diagnosis of HNSCC has increased and nowadays, approximately, 25% of HNSCC patients are aged 70 years and over [7]. Since comorbidities rise steeply with age, patients will became more vulnerable to treatment-related complications. Definitive data to guide treatment decisions among elderly patients is scarce, mainly because patients age 70 years and older are underrepresented in randomized clinical trials, accounting < 10% of enrolling patients [8]. Pretreatment decision-making evaluation, including definition of health status, assessment of social situations and patient preference, becomes paramount to categorize elderly patients and then to define their appropriate management. Whereas in fit older patients treatment approach should be the same as in younger patients and in frail patients a palliative support should be proposed, wild consensus existson the need for a proper treatment selection in vulnerable elderly patients, when standard treatment cannot be tolerated.

Combining the radiobiologic (ended treatment before accelerated repopulation) and logistic (an attractive method to reduce the number of fractions) advantages of hypofractionated RT (HFRT) with the possibility of radiation safety using cetuximab, hypofractionated bioradiotherapy

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(HFBRT) could potentially be an effective therapeutic strategy in these patients, due to decreasing prescription of chemotherapy with age. We designed a study exclusively for vulnerable elderly HNSCC patients. The purpose was to analyze the efficacy and safety profiles of HFBRT in this setting of patients. It is expected that this study will be potentially useful and serve as a reference for a multi-centre randomized controlled clinical trial in evaluating the best treatment approach for vulnerable elderly HNSCC patients in the future.

Materials and methods

Study population

This pilot study was a research project coordinated by Department of Radiological Sciences, Oncology and Pathology, Policlinico Umberto I "Sapienza" University of Rome and it was approved by the scientific institutional ethics committee (number 2936/2017-45). Patients were enrolled after signing an informed consent. Selection criteria included: the elderly (≥ 70 years) able to provide consent for themselves; those with newly diagnosed histologically proven squamous cell carcinoma of the head and neck region; those with clinical T2–4 disease, with or without involved lymph nodes and without distant metastasis at diagnosis. Patients were excluded in case of other histological subtype or a past medical history including another cancer or previous chemotherapy or RT treatment. Clinical examinations, including complete medical history and careful physical examination, as well as nasofibrolaryngoscopy, were combined with radiologic imaging to assess the precise local (T), regional nodal (N), and distant (M) extent of the tumor. Radiologic imaging consisted of head–neck–chest contrast-enhanced computed tomography (CT) with or without head and neck diffusion-weighted magnetic resonance imaging (DW-MRI).

Vulnerability assessment and multidisciplinary evaluation

Patients were stratified according to the mini-cog test and the adult comorbidity evaluation-27 (ACE-27) score [9, 10]. After a careful evaluation, patients were classified as vulnerable in case of reversible conditions, including (i) one or two reversible deficiencies in activities of daily living (ADL), (ii) grade 2 comorbidities, (iii) malnourished status with weight loss of 5–10%, (iv) early cognitive disorders.

Treatment protocol

All patients received HFBRT. RT was delivered with intensity modulate technique at a total dose of 60 Gy (3 Gy/fraction) to the macroscopic tumor volume—both T and N—with 6 to 15 MV energy photons. The prescribed dose was required to cover 95% of the planning target volume. Organs at risk (OARs) were contoured per DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines [11]. Dose constraints (maximum dose, mean dose and dose-volume limits) were defined according to Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) organ-specific paper and the biologically equivalent dose in Gy_3 was calculated [12].

Cetuximab was administered at an initial loading dose of 400 mg/m^2 1 week before HFRT, followed by weekly injections at 250 mg/m^2 during HFRT for a total of 4 weeks of treatment.

Dose modification and follow-up

Toxicity and adverse event assessments were carried out weekly according to the scale of Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [13]. A serious adverse event (SAE) was defined as a clinically significant adverse event including hospitalization or prolongation of hospitalization, life-threatening, death, or causing temporary or permanent severe disability.

RT interruption or delay was permitted for G3 oral mucositis and/or skin toxicity. RT recommencement was allowed once toxicity had resolved to mild/moderate grade. Cetuximab-specific skin and hypersensitivity reactions were treated according to the prescribing information.

During HFBRT, patients were monitored by weekly clinical examination with full hematology, blood biochemistry and liver function tests assessment. After treatment, patients were evaluated with clinical and biological examination at 6-week intervals for the first year, then every 4 months for the next 2 years, and every 6 months thereafter. Overall objective response was evaluated 3 months after the completion of HFBRT by a CT scan or MRI.

End-points and statistical analysis

Primary end-point was to evaluate the objective response rate—defined as complete response and partial response—3 months after the end of the treatment. The criteria used to determine objective clinical tumor response for target lesions included complete response, partial response, progressive disease and stable disease, according to response evaluation criteria in solid tumors (RECIST) guidelines, determined by CT scan or MRI [14].

Secondary end-points included toxicity evaluation, treatment compliance, overall survival (OS) and progression-free survival (PFS). Standard descriptive statistics was used to evaluate the distribution of each factor. OS and PFS were calculated in months from the date of accrual to the date

of the last follow-up, death (OS) and/or progression (PFS). Patients without an event were censored at the last follow-up. The Kaplan–Meier method was used to estimate OS and PFS. Data were processed using R-Studio 0.98.1091 software.

Results

Patient characteristics

A total of six vulnerable patients with locally advanced HNSCC were enrolled in the study. In April 2018, inclusions were suspended after three SAEs and the trial was prematurely stopped. Patient and tumor characteristics are listed in Table 1. Ages ranged from 71 to 82 years, with a median of 77.5 years. At baseline, all patients had a performance status score > 2. The ACE-27 score was 0, 1 and 2 in 1, 2 and 3 patients, respectively. All patients were classified as non-demented at the mini-cog test. Globally, all primary tumor lesions were ≥ 4 cm in the largest diameter and five patients had a positive regional lymph node at diagnosis. HPV-related disease was discovered in one patient only.

Table 1 Patient and tumor characteristics

Characteristic	*n*	%
Age (years)		
Median (range)	77.5 (71–82)	
Gender		
Male	4	66.7
Female	2	33.3
Smoke/alcohol		
Yes	5	83.3
No	1	16.7
Human papilloma virus		
Yes	1	16.7
No	5	83.3
ACE-27 score		
0	1	16.7
1	2	33.3
2	3	50
Mini-cog test		
Demented	0	0
Non-demented	6	100
Site of primary tumor		
Oral cavity	3	50
Oropharynx	3	50
Clinical tumor stage (T)		
T1–2	0	
T3	1	16.7
T4	5	83.3
Clinical nodal stage (N)		
N0	1	16.7
N1	3	50
N2	2	33.3

Treatment compliance and toxicity

All patients completed the programmed treatment. All patients received the IMRT-prescribed total dose of 60 Gy (3 Gy/fraction). Treatment plan did not exceed the normal dose limits. Overall, RT was interrupted for a mean period of 8 days for acute toxicity in three patients. Two patients (33%) received the four planned injections of cetuximab and one patient received the first injection of cetuximab only. All patients had acute toxicity associated with treatment. Details are shown in Table 2. Mucositis and oral pain were the most common acute symptoms. Severe toxic effects were observed in four patients. Three SAEs were observed in three out of six patients.

Response and clinical outcomes

Overall, three patients had an objective response consisting of partial response and three patients had progression disease 3 months after the end of the treatment. The best response—a 90% decrease in the sum of diameters of target lesion—was recorded in the HPV-positive case. No complete response was observed. Median objective partial response duration was 4.5 months (range 3–6). Overall, five deaths were recorded during the follow-up, all but one of related cancer conditions. Two patients presented distant metastasis to bone ($n = 1$) and lung/liver ($n = 1$). Median PFS and OS rates were 2 months and 2.5 months, respectively.

Table 2 Acute toxicity

Acute toxicity	G1–2	G3–4
Constitutional symptoms		
Fatigue	5	
Fever	1	
Dermatology skin		
Radiation dermatitis	1	1
Acneiform eruption	2	3
Gastrointestinal		
Nausea/vomiting		1
Anorexia	2	
Oral mucositis	2	4
Deshydratation	3	
Local pain	5	
Blood count		
Hemoglobin	1	

Discussion

HFBRT showed no benefit in terms of tumor control, but instead showed detriment in terms of toxicity. Although the compliance to the treatment was relatively high (all patients completed RT and two out of six patients received the entire planned cetuximab regimen), the study was stopped because toxicity has been considered a compelling argument to explore alternative hypotheses. Due to the small cohort size, the short follow-up and the severe toxic effects, we agree that our results may not be quantifiable by objective criteria.

Similarly, two previous series, based on limited data set—13 patients with a median age of 68 years (range 52–82) [15]; 18 patients with median age of 65 years (range 44–84) [16]—described more severe toxicities than those reported in the Bonner trial [6]. But, despite different patient population, results cannot be compared because in one trial, RT was delivered to a total dose of 70 Gy in 35 daily fractions [15], and the other was not published in its full text form [16].

Until now, to our knowledge, no randomized studies, as well as no retrospective series had been completed in vulnerable elderly HNSCC patients. This is the first study that evaluate cetuximab in combination with HFRT in the context of this patient population. As *vulnerable patient* is a relatively new category in HNSCC since the actual extension of the lifespan, there should be changes in its treatment algorithm. We defined vulnerable patients according to two screening tools easily integrated into clinical practice—the mini-cog test and the ACE-27 score—[9, 10]. These tools guarantee a pretreatment evaluation of the most common physiological side effects of aging, physical and mental ability and identify those elderly patients who require further multidimensional geriatrician assessment. A cognitive function <4 and a comorbidity index of 2 define a vulnerable patient. Many other screening tools have been developed for this indication, each with different component factors [17]. For instance, the national comprehensive cancer network (NCCN) panel refers to ACE-27 and health-related scales—the University of Washington quality of life (QoL) scale (UW-QoL); the European organization for research and treatment of cancer QoL questionnaire (EORTC-QLQ-H&N35); the functional assessment of cancer therapy head and neck module (FACT-H&N)—to define patients' comorbidity and QoL, respectively [1]. At present, there is no consensus on what the best screening tool should be and there is no robust evidence to support its influence on treatment choice. But, it is clear that establishing whether an elderly patient is fit, vulnerable or frail is paramount to properly select the best management.

Similarly, there is scarce data on how to treat elderly HNSCC patients. Usually randomized clinical trials included only fit patients, due to strict inclusion criteria mainly based on performance status and comorbidities. Therefore, geriatric treatment strategies are primarily extrapolated from recommendations designed for younger and fitter patients. In the meta-analysis of chemotherapy in head and neck cancer (MACH-NC), the subgroup analysis of the effect of chemotherapy on survival according to patient age showed a significant decreasing effect of chemotherapy with increasing age, suggesting that cisplatin led to inferior results [5]. But it is not possible to rule out definitive conclusions. In fact, despite the dilution effect, only 1225 (7.8%) of the 15,703 randomized patients to loco-regional treatment plus concomitant chemotherapy versus loco-regional treatment alone were 71 and over.

Retrospective studies in elderly HNSCC patients have shown that (i) induction chemotherapy, using docetaxel 70 mg/m^2 and cisplatin 75 mg/m^2, yielded a good response rate and tolerable toxicity [18], (ii) standard CRT showed superior survival rates compared to suboptimal treatment [19], (iii) definitive RT with concurrent cetuximab or cytotoxic chemotherapy is associated with a significant increase in OS compared to radiation alone [20]. This suggests that, in elderly patients, a curative treatment should be offered whenever possible because concomitant platinum-based chemotherapy or cetuximab infusion appear to improve the effect of radiation therapy. Anyway, both direct and indirect comparisons should be interpreted with caution due to the hypothesis-generating results, the low number of patients and the difference in patient population studied. The main limit is the heterogeneous elderly definition fixed by different chronological cut-offs and the lack of elderly categorization.

Our study was originally designed to test whether HFBRT effectively improves objective clinical response minimizing treatment-related toxicity and reducing total treatment time in vulnerable elderly with HNSCC. We used cetuximab as this drug is widely accepted and is recommended by international guidelines as one of the appropriate options in HNSCC management [1]. This was potentially considered an advantage, because chemotherapy is not constantly applicable in vulnerable patients. But this approach was not easily feasible and the magnitude of its benefit was less than expected. Prospective studies testing different approaches for vulnerable elderly HNSCC patients should be preformed. In light of our experience, we would advise caution with HFBRT strategies in vulnerable elderly, and strongly advocate a multi-institutional trial to better define routine clinical management in this setting of patients.

Conclusion

Treatment of vulnerable elderly HNSCC patients should be patient-centered and a specific treatment algorithm to guide decision-making should be proposed. Standard management for this setting of patients remains to be defined. Further prospective trials specifically designed to vulnerable elderly HNSCC population should be carried out to propose definitive conclusions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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