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Review

Systemic treatment and medical management of metastatic squamous cell carcinoma of the head and neck: Review of the literature and proposal for management changes

Frédéric Peyrade [a,*], Didier Cupissol [b], Lionel Geoffrois [c], Frédéric Rolland [d], Christian Borel [e], Catherine Ciais [f], Sandrine Faivre [g], Joël Guigay [h]

[a] Department of Medical Oncology, Centre Antoine Lacassagne, Nice, France
[b] Department of Medical Oncology, Centre Val d'Aurelle, Montpellier, France
[c] Department of Medical Oncology, Centre Alexis Vautrin, Vandoeuvre-les-Nancy, France
[d] Department of Medical Oncology, Institut Cancérologique de l'Ouest, Nantes Saint-Herblain, France
[e] Department of Medical Oncology, Centre Paul Strauss, Strasbourg, France
[f] Department of Supportive Care, Centre Antoine Lacassagne, Nice, France
[g] Department of Medical Oncology, Hôpital Beaujon, Paris, France
[h] Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France

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SUMMARY

Objective: Worldwide, head and neck carcinomas account for 5% of all malignancies. Two-thirds of patients relapse after initial multimodal therapy. Until early 2000, the median overall survival (OS) of metastatic patients was about 6 months. Recently, new drugs have been incorporated in patient management, thus enabling an increase in OS. This review aims to define the comprehensive medical management of patients with relapsing head and neck carcinoma.
Methods: A comprehensive review of the literature was made targeting four topics: first- and second-line treatment, supportive care, and management of elderly patients.
Results: The choice of first- or second-line treatments is mainly based on performance status. In the elderly, geriatric assessment could be helpful. For PS 0.1 patients, the standard first-line treatment is 6 cycles of cisplatin-5FU-cetuximab. In the event of response, cetuximab alone is prolonged until progression or unacceptable toxicity. For second-line treatment, several options are currently available: enrolment in clinical trials, single-agent therapy (methotrexate, taxane, cetuximab), and best supportive care (BSC). Supportive care has to be initiated very early in the course of the disease to prevent pain, dysphagia and malnutrition. In elderly patients, the therapeutic options are: first-line treatment with the EXTREME regimen replacing cisplatin by carboplatin for patients in good general condition or methotrexate alone for other patients. BSC continues to be given to all patients (i.e. poor general conditions).
Conclusion: In spite of numerous pending issues requiring further investigation, these recommendations seem to be routinely applicable.

Introduction

Worldwide, carcinomas of the head and neck (CHN) account for more than 5% of all malignancies, which are squamous cell carcinomas (SCCHN) in 90% of cases.[1] Despite multimodal treatment, 50–60% of patients with stage III or IV disease relapse locoregionally. Of these, most are not suitable for surgery or radiotherapy, or develop distant metastases.[2]

Until recently, no chemotherapy regimen had demonstrated survival improvement in recurrent or metastatic SCCHN (MSCCHN). In terms of efficacy, only the cisplatin/5-fluorouracil regimen (PF) seemed to improve the overall response rate (ORR).[3,4] In the 1990s, the PF regimen was considered the first-line standard treatment for MSCCHN. The recent introduction of targeted therapies has modified first-line treatment as cetuximab has demonstrated significant activity in combination with platinum-based chemotherapy compared with platinum-based therapy.[5] This improvement raises the question of second-line therapy as this situation is becoming more and more frequent. after the first relapse, life expectancy is usually poor and quality of life (QoL) is highly impaired requiring early and highly efficient supportive care.[6–8]

* Corresponding author. Address: Département d'Oncologie Médicale, Centre Antoine Lacassagne, 33 Avenue de Valombrose, 06186 Nice Cedex 2, France. Tel.: +33 (0)4 92 03 10 47; fax: +33 (0)4 92 03 15 92.
E-mail address: frederic.peyrade@nice.unicancer.fr (F. Peyrade).

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Another issue in the management of MSCCHN is the increasing number of patients aged 70 years and over. Elderly patients are underrepresented in clinical trials, thus making it difficult to perform similar standard protocols with these patients.

The aim of this review was to make a comprehensive review of the literature regarding the systemic treatment (i.e. without radiotherapy) and medical management of MSCCHN in order to establish proposals designed to clarify and simplify therapeutic behaviors. In order to achieve a global approach to MSCCHN disease, four topics were discussed: first-line treatment, second-line treatment, supportive care and elderly patients.

Methods

Literature review and analysis

Four topics were targeted: first-line MSCCHN treatment, second-line MSCCHN treatment, supportive care, and management of elderly patients.

Electronic and manual searches including Medline and The Cochrane Library (search terms: metastatic, squamous cell carcinoma of the head and neck, clinical trial) and abstracts published in the proceedings of meetings of the American Society of Clinical Oncology, the European Conference of Clinical Oncology, and the European Society of Medical Oncology were used to identify relevant literature. To ensure a systematic review of the literature on the management of patients with MSCCHN, articles were selected for inclusion if they met the following criteria: (i) randomized controlled trials (RCTs) with appropriate control groups, or (ii) meta-analyses of RCTs in patients with MSCCHN. Data from phase II clinical trials or retrospective analyses were considered only if there was no evidence from randomized phase III clinical trials.

All co-authors are full-time head and neck medical oncologists. All helped in the preparation of the draft guideline document, which was then regularly distributed for review by the entire panel. The final text was approved by all participants.

First-line treatment

Before targeted therapies

For first-line treatment, we found numerous phase II studies, which evaluated various single-agent cytotoxic drugs including methotrexate, bleomycin, cisplatin, carboplatin, 5-fluorouracil (5FU), paclitaxel, and docetaxel. However, reported response rates have to be interpreted cautiously as the evaluation methods used in these previous studies do not meet the current criteria. In contrast, there are few randomized phase III trials. Although platinum-based chemotherapy was a standard approach and resulted in higher response rates than monotherapy, combination regimens did not provide a survival benefit compared to monotherapy in randomized trials of recurrent or metastatic (R/M) SCCHN. Polychemotherapy, especially with cisplatin-based regimens, was associated with a higher level of toxicity as compared with monotherapy.

In the 1990s, the standard treatment was the PF regimen. Although polychemotherapy proved superior in terms of ORR, several trials showed inconclusive results for overall survival (OS) (Table 1).[3,4,9,10] Interestingly, with the PF regimen, continuous infusion of 5FU led to better results than bolus.[11] On the other hand, single-agent paclitaxel, delivered weekly or every 3 weeks, did not demonstrate superiority compared with single-agent methotrexate.[12] As regards the choice of platinum salt, while cisplatin seemed to provide a better ORR than carboplatin, it did not improve OS.[4]

Table 1
Results of randomized trials in first-line treatment of metastatic carcinoma of the head and neck.[3,4,9,10]

Authors	*N*	Regimen	ORR, %	Median survival, months
Jacobs et al.[3]	249	PF	32^{S}	5.5^{NS}
		P	17	5.0
		F	13	6.1
Forastiere et al.[4]	277	PF	32^{S}	6.6^{NS}
		CF	21	5.0
		M	10	5.6
Clavel et al.[9]	382	PMBV	34^{S}	7.0^{NS}
		PF	31^{S}	7.0
		P	15	7.0
Gibson et al.[10]	218	PF	27^{NS}	8.7^{NS}
		PT	26	8.1

P, cisplatin; F, 5-fluorouracil; C, carboplatin; M, methotrexate; B, bleomycin; V, vincristine; T, paclitaxel; S, significant difference; NS, non-significant difference.

Docetaxel-based chemotherapy, either as single-agent or as part of doublet- or triplet-chemotherapy regimens (docetaxel-PF [TPF]), demonstrated activity in R/M SCCHN. Docetaxel-based regimens have shown promising progression-free survival (PFS) and OS rates, but were associated with an increase of grade III hematological and infectious toxicities, indicating that further phase III trials with docetaxel-containing regimens are warranted.[13,14]

The advent of targeted therapies

The epidermal growth factor receptor (EGFR) is upregulated in 90% of head and neck tumors. This overexpression is associated with poor prognosis. Inhibition of EGFR pathway by a monoclonal antibody gave rather disappointing results. Cetuximab, a chimerical immunoglobulin G1 (IgG1) anti-EGFR, was studied in refractory patients combined with platinum salts (cisplatin or carboplatin) in order to reverse resistance to platinum salts. However, single-agent cetuximab exhibited similar activity to platinum salt in refractory MSCCHN with an ORR of 13%, a median PFS of 2.3 months, and a median OS of 5.9 months.[15]

A first trial comparing cisplatin–cetuximab to cisplatin–placebo showed poor results, but the low number of enrolled patients ($n = 117$) did not allow sufficient statistical power.[16] More recently, the EXTREME trial has demonstrated the significant benefit of adding cetuximab to the PF regimen, then followed by cetuximab as maintenance therapy, in comparison with PF alone in first-line treatment of MSCCHN.[5] The ORR increased by 83%, the PFS was prolonged from 3.3 to 5.6 months (hazard ratio [HR] = 0.54; $P < 0.001$), and the OS was improved by 2.7 months (10.1 months *versus* 7.4 months; HR = 0.797; $P = 0.036$). The prognostic factors were unchanged since general status, weight loss, local relapse occurring in the irradiated area, disease-free interval, and tumor differentiation were found to be significant. Recently, Guigay and colleagues[17] reported the final results of TPEx protocol as first-line treatment for metastatic patients. In this phase II study, 52 patients were included and were treated with a combination of cisplatinum, docetaxel and cetuximab for 4 cycles followed by cetuximab alone (500 mg/m^2 D1 = D15). The median OS was 14 months and 59% of patients were alive at 1 year. However, further phase III studies are required in order to compare these findings with the EXTREME combination.

Other targeted therapies have been evaluated in MSCCHN and several targets have been tested. In former years, the tyrosine kinase inhibitors gefitinib and erlotinib were widely used. Single-agent erlotinib provided an ORR of 4.3%, and a median OS of 6 months.[18] Gefitinib (500 mg/day) was compared to