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Journal of Cancer Research and Cellular Therapeutics
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Research Article

Weekly Carboplatin, Paclitaxel and Cetuximab with Pembrolizumab Every 3 Weeks Is Active and Tolerated in Patients with Locally Advanced and/or Metastatic/Recurrent Head and Neck Squamous Cell Carcinoma

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Received date: February 08, 2024; **Accepted date:** February 16, 2024; **Published date:** February 26, 2024

Citation: Bruno CHAUFFERT, Marion GOGNARD, Abdenour OUIKENE, Mohamad CHEHIMI, Agnes GALEZ et. al., (2024), Weekly carboplatin, paclitaxel and cetuximab with pembrolizumab every 3 weeks is active and tolerated in patients with locally advanced and/or metastatic/recurrent head and neck squamous cell carcinoma, *J Cancer Research and Cellular Therapeutics*, 8(1); **DOI:10.31579/2640-1053/185**

Abstract

The management of recurrent/metastatic head and neck carcinoma (R/M HNSCC) is evolving with new available molecules and combination modalities. Anti-EGFR cetuximab and immune checkpoint inhibitors (ICI) are used either alone or in combination with conventional platinum-based doublet chemotherapy (with taxanes or fluorouracil). Few data have been reported on the combination of doublet chemotherapy with both cetuximab and ICI. Here, we review a series of 17 patients that received a quadritherapy (QT) with paclitaxel, 60 mg/m2/week, carboplatin, AUC 1.5/week, cetuximab, 250 mg/m2 /week, and pembrolizumab, 200 mg every 3 weeks. Nine to 12 weekly injections were done before evaluation by clinical examination and PET-CT. Nine patients with bulky advanced disease responded to QT (3 complete responses (CR), 6 partial responses (PR)). Seven patients further received a cisplatin-based chemoradiotherapy (CRT). Eight out of nine patients are still in CR. Eight patients received QT for recurrent and/or metastatic disease. One CR, 3 PR and 3 stable diseases were recorded. Adverse events were minor, except for an ICI-related grade 3 cardiac toxicity. Overall, this short series indicates that QT with weekly carboplatin-paclitaxel-cetuximab and pembrolizumab every 3 weeks is safe and active in patients with advanced or R/M HNSCC. These results should be confirmed through further randomized trials.

Keywords: pembrolizumab; cetuximab; paclitaxel; carboplatin; head and neck squamous cell carcinoma

Introduction

Head and neck squamous cell carcinoma (HNSCC) are usually treated with curative intention by surgery and/or concomitant chemoradiotherapy (CRT). However, a fraction of patients will relapse with distant metastases and/or locoregional recurrence. About 5% of patients present with upfront metastases [1]. In some cases, patients present with a bulky local and/or regional disease, mostly cervical nodes. The TPF regimen (docetaxel, cisplatin and fluorouracil) is then used as a neodjuvant approach before CRT (2). However, TPF is not well tolerated and cannot be used in frail patients. The EXTREME protocol (cisplatin or carboplatin, fluorouracil, and cetuximab, followed by weekly cetuximab maintenance) is still considered to be the standard first-line treatment for R/M HNSCC [3]. However, the side effects of six cycles of EXTREME limit its administration to fit patients. The TPEX protocol (cisplatin-docetaxel-cetuximab) for 4 cycles and cetuximab maintenance did not improve the overall survival, but it led to fewer toxicities than the EXTREME protocol [4]. The non-inferiority and better tolerance of

carboplatin-paclitaxel-cetuximab compared to the EXTREME regimen was reported [5]. After decades of therapeutic stagnation, immunotherapy has transformed the field of cancer therapeutics. The KEYNOTE-048 phase III study established that pembrolizumab, an anti-PD1 antibody, plus standard chemotherapy with platinum and 5-fluorouracil is an appropriate first-line treatment for R/M HNSCC [6]. However, only 15-20% of patients ultimately benefit from anti-PD1 alone or in combination with chemotherapy, highlighting the need to improve the efficacy of immune checkpoint inhibitors for HNSCC treatment. A phase II trial reported that the combination of pembrolizumab and cetuximab is active and safe [7]. However, combinations of the most active agents in HNSCC, such as platinum-based doublet with taxane combined with cetuximab and cisplatin is a option to explore. Last year, we published a case series on 8 patients that received carboplatin-paclitaxel-cetuximab-pembrolizumab (quadritherapy) using a 3 weekly regimen [8]. The response rate was impressive (8/8) in selected patients. We have modified the protocol so that it was suitable for all patients, particularly frail patients, by using weekly carboplatin, paclitaxel, cetuximab and pembrolizumab every 3 weeks. The aim of the present study is to report the results of this new regimen on a series of 17 consecutive patients, with locally advanced or metastatic/recurrent disease.

Methods

Patients were treated at our institution from March 2022 to December 2023. All patients had pathologically confirmed HNSCC and were not immediately suitable for curative therapy (surgery and/or CRT). None had been treated before, except for patients that had disease recurrence after previous radiotherapy with concomitant cisplatin or carboplatin. All patients were smokers and had a negative p16 status. The PD-L1 score was not taken into account for the prescription of pembrolizumab. Patients were informed by the investigators about the exploratory aspect of this regimen. Treatment was validated by the specialized medical committee for head and neck carcinomas in our institution. Weekly quadruplet (termed hereafter QT) consisted of paclitaxel (60 mg/m2/wk), carboplatin (AUC 1.5 mg/mL/min/wk) and cetuximab (250 mg/m2/wk). Pembrolizumab (200 mg) was given every 3 weeks. All drugs are approved and available in France for R/M HNSCC. Patients received 9 to 12 weekly injections before evaluation by clinical examination with nasofibroscopy and positron emission tomography-computed tomography (PET-CT). Tumor response was scored both by RECIST [9] and PERCIST score [10], for clinical evaluation and PET-CT, respectively. If stable, partial or complete response was observed, pembrolizumab 200 mg was pursued every 3 weeks until progression in reccurent/metastatic patients. In patients with locally advanced disease at the initial time, radiotherapy with either cisplatin or carboplatin was done with no further treatment.

Results

17 consecutive patients received QT. Nine had a locally advanced disease not allowing for initial CRT due to large tumor volume (Table 1). All tumors responded (6 PR, 3 CR) to induction QT, so that a CRT with concomitant cisplatin or carboplatin could be completed in 7/9 patients. One patient in CR refused RT. Radiotherapy was unfeasible for a patient with a neck deformation. Clinical response was quickly observed, most often after a month of QT. All patients are alive without disease on December 31, 2023.

	Gender (Age)	Localization (TNM)	Toxicity of QT (grade)	Response after QT	Response after CRT	Overall survival (months)
1	M (50)	Basis of tongue (T3N2M0)		CR	CR	18 (+)
2	M (61)	Pelvilingual cervical nodes (T4N2M0)		PR	CR	16 (+)
3	M (64)	Maxillary sinus (T4NOM0)		PR	CR	15 (+)
4	M (73)	Oropharynx, cervical, mediastinal nodes (T2N3M1)	skin (2)	PR	CR	7 (+)
5	M (49)	Larynx, cervical nodes (T3N1M0)		CR	CR	7 (+)
6	F (66)	Pharynx, cervical nodes (T4N2M0)		PR	PR	6 (+)
7	F (67)	Pelvilingual, cervical nodes (T3N2M0)	skin (2), cardiac (3)	CR	RT not done	6 (+)
8	M (76)	Larynx, cervical nodes (T2N3M0)		PR	CR	5 (+)
9	M (70)	Cervical nodes (T0N3M0)		PR	RT not done	5 (+)

Figure 1: Results of neo-adjuvant use of weekly quadritherapy (QT).

CR: complete response. PR: partial response.CRT: chemoradiotherapy. +: indicates that patients are alive on December 31, 2023.

Six patients had local recurrence and/or metastases after previous CRT and 2 patients had initial metastases (Table 2). One complete response, 3 partial responses and 3 stable diseases were observed. Only one patient had progression on QT. Four patients out of eight were alive on December 31, 2023. Three had persistent disease and received a second line of treatment.

Gender (age)	Initial localization (TNM)	Previous treatment	Site of recurrence/metastases	Toxicity (grade)	Best response after QT	Time of Disease Control by QT then pembro-lizumab maintenance (months)	Overall Survival (months)
M (69)	Pelvilingual (T3N2M0)	RT / cisPt	local, lung		SD	14	17 (+)

M (72)	Pelvilingual (T4N1M0)	RT/carbopt	local, lung		PR	15 (+)	15 (+)
M (45)	Oropharynx (T3N2M0)	RT/cisPt	local, lung		CR	6	13 (+)
M (57)	Pharynx (T3N0M1)		local, mediastinal lombo-aortic nodes	skin (1)	PR	8	10 (D)
M (64)	Larynx (T4N2M0)	RT/carboPt	local, lung, mediastinal	skin (2)	PR	4	5 (D)
M (55)	Larynx (T4N0M0)	Surgery + RT	lung	skin (2)	SD	7	7 (+)
M (86)	Cervical nodes (T0N3M0)		lung, mediastinal nodes		PROG	2	5 (D)
M (56)	Oropharynx (T3N2M0)	RT/cispt	lung, mediastinal nodes	skin (1)	SD	3	4 (D)

Table 2: Results of weekly QT in patients with recurrent and/or metastatic disease.

Cispt: cisplatin. Carbopt: carboplatin. CR: complete response. PR: partial response. SD: stable disease. PROG: progressive disease. D indicates that patients are dead. + : indicates that patients are alive on December 31, 2023.

Six patients had grade1- 2 cutaneous toxicity related to cetuximab. Oral cyclin antibiotic and local steroids permitted the continuation of the regimen. A pembrolizumab-related cardiac grade 3 myocarditis was recorded in a female patient with increased levels of troponin and 20% decrease of the ventricular ejection fraction. Cardiac toxicity was reversible with steroids after discontinuation of pembrolizumab. No other toxicity related to the immune checkpoint inhibitor (ICI) therapy occurred. No major hematological toxicity occurred due to the low doses of weekly carboplatin and paclitaxel. In some cases, there was a one week deferral of the planned cure and use of granulocyte stimulating factor.

Discussion

The present series presents results from a new weekly regimen of paclitaxel, carboplatin, cetuximab with concomitant pembrolizumab as ICI. The complete or partial response rate was higher in the neo-adjuvant cohort (9/9) than in patients with recurrence and/or metastases (4/8). Only 1 patient had progressive disease on QT. Toxicity was low, except for a reversible grade III myocarditis related to pembrolizumab. Hematological tolerance was good due to the weekly regimen of carboplatin and paclitaxel. The lower toxicity of weekly carboplatin and paclitaxel, in combination with cetuximab, with equivalent efficacy to a tri-weekly administration that was reported earlier [11]. By comparison, the response rates for standard protocols were 36% and 59% in the EXTREME (platinum salt, fluorouracil, cetuximab) and TPEx (docetaxel, platinum salt, cetuximab) trials, respectively [3,4]. In the keynote-048 study, response rate to pembrolizumab monotherapy was 17%, which increased to 36% when pembrolizumab was combined with a standard cisplatin/fluorouracil chemotherapy regimen [7].

Triplet therapy with a taxane, carboplatin and cetuximab had soon been explored with encouraging results [12]. The triplet was used in a neoadjuvant setting in a case series of 24 previously untreated patients, who were unfit to receive the TPF protocol [13]. The response rate was 87% after 3 cycles of the PCE protocol, and some patients benefited from a locoregional curative treatment. Carboplatin, paclitaxel, and cetuximab were also used on a weekly regimen with a good tolerance in frail patients with R/M HNSCC. A 43% overall response rate was recorded in 60 patients [14].

Triplet of paclitaxel, carboplatin and an ICI were also investigated. Safety and preliminary activity of pembrolizumab and weekly carboplatin-paclitaxel were evaluated in 8 heavily pretreated and/or fragile patients with recurrent/metastatic head and neck cancer. Disease control rate was 43%, with little toxicity [15].Neoadjuvant chemo-immunotherapy with carboplatin, nab-paclitaxel, and durvalumab produced a 57% response rate in patients with resectable locally advanced HNSCC [16].

Few quadruplets of chemotherapy with both cetuximab and an ICI have been reported. Weekly paclitaxel, carboplatin, cetuximab (PCE) followed by nivolumab as ICI led to a 48% response rate in recurrent/metastatic HNSCC patients. However, ICI was used following but not concomitantly with chemotherapy and cetuximab [17]. At our knowledge, we were the first to report a high response rate (8/8) with a concomitant quadruplet using 3 weekly administration of paclitaxel, carboplatin pembrolizumab with weekly cetuximab [8]. The present series on 17 new patients confirm the high response rate to a weekly quadruplet and its good tolerance.

Activation of sustained innate immunity by cetuximab through NK activation and antibody-dependent complement cytotoxicity (ADCC) could explain its synergy with the PD1 inhibitors, as was for example reported in NSCLC patients [18].

Conclusion

Our second series confirmed that quadritherapy seems active and tolerated in the first-line treatment of locally advanced, or recurrent/metastatic HNSCC. The additive role of combining an anti-PD1 antibody to a paclitaxel/carboplatin/cetuximab backbone should be investigated in prospective randomized trials.

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DOI:10.31579/2640-1053/185