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Original Research

Response to salvage chemotherapy after progression on immune checkpoint inhibitors in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck

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Abstract ***Background:*** Immune checkpoint inhibitors (ICI) are active in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). Recent data suggest that exposure to ICI improves response to salvage chemotherapy (SCT) in advanced non–small-cell lung cancer. We evaluated response to chemotherapy in patients who had progressed on ICI in patients with R/M SCCHN.
Patients and methods: A retrospective study was conducted at 4 French centres. Eligibility criteria were patients who progressed after treatment with ICI for R/M SCCHN and received SCT and for whom efficacy data were available between September 2014 and January 2018.
Results: Of 232 patients treated with ICI, 82 met eligibility criteria: 84% were male. ICI was given as monotherapy in 45% of patients or as combination in 55%. SCT included taxanes

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(56.1%), cetuximab in combination with taxanes or platinum (50%), platinum-based regimen (36.6%). The median number of treatment lines before SCT was 2 (range 1–6). The objective response rate (ORR) to SCT was 30%. Three patients (4%) presented complete response and 22 patients (27%) had partial response. Median progression-free survival was 3.6 months and median overall survival was 7.8 months. The age at SCT, initial tumour location, number of prior chemotherapy regimens, type of chemotherapy before ICI, best response to ICI, site of relapse and Eastern Cooperative Oncology Group at SCT were not associated with response to SCT on univariate analysis.

Conclusion: In R/M SCCHN, the ORR to SCT was high (30%) suggesting that exposure to ICI may increase tumour sensitivity to chemotherapy.

1. Introduction

Patients with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) have a dismal prognosis with a median overall survival (OS) of less than one year [1]. The EXTREME regimen combining 5-flurouracil, cisplatin and cetuximab is the most common regimen used in first-line setting in patients with a median OS of 10.1 months, median progression free-survival (PFS) of 5.6 months and an objective response rate (ORR) of 36% [2]. Until 2016, there was no standard of care beyond first-line therapy. Cetuximab, taxanes and methotrexate may be used alone or in combination as second-line treatment with an ORR ranging from 6 to 13% and median OS between 3 and 6 months [3–5]. Immune checkpoint inhibitors (ICI) showed efficacy in the treatment of patients with R/M SCCHN who relapsed after a platinum-based chemotherapy regimen. Nivolumab and pembrolizumab, fully humanized programmed death-1 (PD-1) inhibitors, were associated with an ORR of 13–18% in second-line setting and were approved by the FDA in the treatment of R/M SCCHN with disease progression on or after a platinum-based therapy [6,7]. The CheckMate-141 trial which compared nivolumab to single-agent chemotherapy in second-line setting showed no significant improvement in PFS in the nivolumab group (2.0 vs 2.3 months in the chemotherapy arm; hazard ratio [HR] for disease progression or death, 0.89; 95% confidence interval (CI), 0.70 to 1.13; $p = 0.32$), but a significantly higher OS (7.5 months vs 5.1 months; HR for death, 0.70; 97.73% CI, 0.51 to 0.96; $p = 0.01$) [6]. The Keynote-040 trial which compared pembrolizumab to single-agent chemotherapy in R/M SCCHN showed the same findings with a median OS with the intention to treat population of 8.4 months with pembrolizumab and 6.9 months with standard of care (HR for death, 0.80; 95% CI, 0.65–0.98; nominal $p = 0.0161$) [7]. This survival pattern was observed in several trials of ICI in non–small-cell lung cancer (NSCLC) and metastatic urothelial cancer in which there was no benefit of immunotherapy in terms of PFS and a significantly longer OS in the ICI arms [8–10]. This can be explained, at least in part by the increased sensitivity to chemotherapy after ICI. In fact, recent data showed that salvage chemotherapy (SCT) after progression on ICI was associated with higher ORR than historical data did in NSCLC, metastatic urothelial cancer and classical Hodgkin lymphoma (cHL) [11–13]. We aim to evaluate whether this increased sensitivity to SCT was also observed in R/M SCCHN by measuring the response rate associated with SCT after progression on ICI in a retrospective cohort of R/M SCCHN patients.

2. Materials and methods

2.1. Study design and patients

This study was conducted in 4 French centres (Gustave Roussy, Villejuif; Centre Antoine Lacassagne, Nice; University hospital of Bordeaux; Institut Curie, Paris). We retrospectively reviewed data concerning all consecutive patients with R/M SCCHN and treated with ICI between September 2014 and January 2018. All patients received immunotherapy in clinical trials. Eligibility criteria were patients with histologically proven SCCHN, treatment with ICI, documented radiological progression after treatment with ICI (primary or secondary resistance to ICI), treatment with SCT and availability of efficacy data defined as radiological evaluation or death or clinical evidence of disease progression before radiological evaluation. Clinical and radiological data and outcome were collected from review of medical records.

2.2. End-points

The primary endpoint was the ORR to SCT according to guidelines of the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). The secondary end-points were PFS defined as the time between the

starting date of SCT and tumour progression or death due to any cause and OS defined as the time between the start of SCT and death due to any cause. Patient evaluation was carried out using computed tomography (CT) scan according to the policy of each centre (range: 8–12 weeks).

2.3. Statistical analysis

ORR associated with SCT and its 95% CI were calculated. Associations between patient, tumour, treatment characteristics and ORR were tested using chi-square test or Fisher exact tests according to sample size. Follow-up was estimated with the reverse Kaplan–Meier method. OS and PFS were estimated using the Kaplan–Meier method. Univariate analysis was performed using log-rank test. Cox model was used for multivariate analysis.

3. Results

3.1. Patients' characteristics

From September 2014 to January 2018, we identified 232 patients who were treated with ICI for R/M SCCHN. Fifty-six patients continued ICI, 84 patients dead or had poor performance status, and ten patients were not included (5 patients were lost to follow-up after progression on ICI and received SCT on another centres and 5 patients begun their SCT at the cutoff date defined as 15 January 2018). Eighty-two patients met eligibility criteria and were included in the analysis (Fig. 1). Their baseline characteristics are summarized in Table 1.

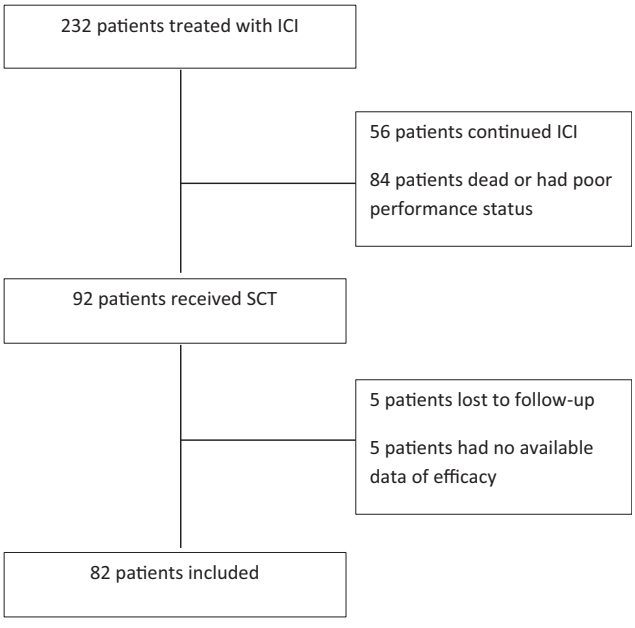

Fig. 1. Flow chart. ICI: immune checkpoint inhibitor; SCT: salvage chemotherapy.

Table 1
Patients' characteristics.

Patients	N = 82 (%)
Age, median at diagnosis (range)	58 (23–83)
Sex	
Male	69 (84%)
Female	13 (16%)
Localization	
Oropharynx	28 (34%)
Hypopharynx	21 (26%)
Oral cavity	19 (23%)
Larynx	13 (16%)
Unknown	1 (1%)
Type of relapse	
Locoregional	34 (41%)
Distant	25 (31%)
Locoregional + distant	23 (28%)
Number of lines before ICI	
0	20 (24%)
1	43 (53%)
2	14 (17%)
≥3	5 (6%)
Prior line to ICI	
Platinum-based CT	50 (61%)
Taxane	9 (11%)
Other	3 (4%)
No prior line	20 (24%)
Best response to prior line	
CR	1 (%)
PR	30 (37%)
SD	16 (20%)
PD	13 (16%)
Unknown or no prior line	21 (26%)

ICI: immune checkpoint inhibitors, CT: computed tomography, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease.

Twelve patients (15%) had metastatic disease at diagnosis. Data concerning efficacy of ICI were not presented because all patients were treated in clinical trials. Thirty-seven patients (45%) received ICI as monotherapy: PD-1 inhibitor (n = 30), or programmed death-ligand 1 (PD-L1) inhibitor (n = 5) or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor (n = 2) and 45 patients (55%) as combination: PD-1 inhibitor and CTLA-4 inhibitor (n = 16) or PD-1 inhibitor and killer-cell immunoglobulin-like receptor inhibitor (n = 29). The median number of treatment lines, including SCT, was 3 (range 2–8). Patients received a median number of 2 treatment lines before SCT (range 1–6).

3.2. Salvage chemotherapy

The median age at SCT was 60 years (range 24–84). The median time between last dose of ICI and the start of SCT was 1.0 month (range 0.3–2.5 months). SCT was administered as second-line treatment (n = 20, 24%), third-line (n = 43, 53%), fourth-line (n = 14, 17%), fifth-line (n = 3, 4%), sixth-line (n = 1, 1%) and seventh-line (n = 1, 1%). Forty-six patients (56%)

received taxanes as SCT, 26 of them as monotherapy (paclitaxel or docetaxel alone), 17 of them in combination with cetuximab ± platinum and 3 in combination with platinum. Thirty patients (37%) received platinum-based regimen as SCT (9 patients with cisplatin and 21 with carboplatin): 16 patients of them were treated with EXTREME regimen, 3 of them with TPEx (docetaxel, platinum and cetuximab), 8 with carboplatin and cetuximab and 3 patients with carboplatin and paclitaxel.

3.3. Efficacy of salvage chemotherapy

The ORR to SCT was 30% (95% CI, 21%–40%). Three complete responses (4%) have been observed and 22 partial responses (27%). The disease control rate was 57% (95% CI, 46%–68%). With a median follow-up of 11.5 months (range 4.8–31.4 months), 27 patients were alive at last follow-up. The median PFS was 3.6 months (95% CI, 2.6–5.1) and the median OS was 7.8 months (95% CI, 5.3–10.8) (Fig. 2).

The ORR to SCT was 40% in patients who received ICI as first-line therapy compared with 27% in patients who received ICI as second-line treatment or more ($P = 0.29$). The age at SCT, initial tumour location, number of prior chemotherapy regimens, type of chemotherapy before ICI, best response to ICI, site of relapse and Eastern Cooperative Oncology Group (ECOG) at SCT were not associated with response to SCT on univariate analysis (Table 2). There was no significant difference in terms of median PFS (5.2 months vs 3.4 months, $P = 0.14$) and median OS (12 months vs 7.6 months, $P = 0.36$) in patients who received ICI as first-line treatment and patients who received ICI as second-line therapy or more. The combination of cetuximab + taxane ± platinum was associated with higher ORR than other chemotherapy regimens (53% vs 25%, $P = 0.024$). The univariate analysis showed that type of CT before ICI, best response to ICI and ECOG at the beginning of the SCT were prognostic factors for PFS and OS (Table 3). In multivariate analysis, type of CT before ICI, best response to ICI and ECOG at SCT were prognostic factors for PFS. However, best response to ICI and ECOG at SCT were the only prognostic factors for OS (Table 4).

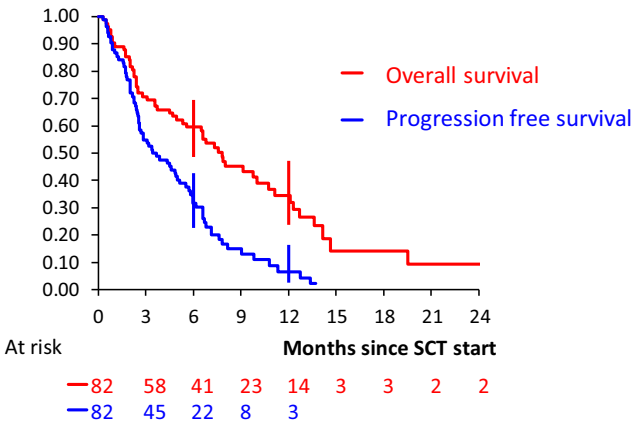

Fig. 2. PFS and OS after SCT. PFS: progression free-survival; OS: overall survival; SCT: salvage chemotherapy.

Table 2
Prognostic analysis of ORR after SCT: univariate analysis.

Patients	SD–PD	CR–PR	*P* value
Age at progression after immunotherapy			0.47
<60 years	27 (66%)	14 (34%)	
≥ 60 years 30 (73%) 11 (27%)			
Initial tumour location[a]			0.55
Oropharynx	22 (79%)	6 (21%)	
Hypopharynx	13 (62%)	8 (38%)	
Oral cavity	12 (63%)	7 (37%)	
Larynx	9 (69%)	4 (31%)	
Number of treatment lines before immunotherapy			0.45
0	12 (60%)	8 (40%)	
1	30 (70%)	13 (30%)	
2	10 (71%)	4 (29%)	
3 to 5	5 (100%)	0 (0%)	
Type of chemo of the line before immunotherapy			0.48
Platinum based	35 (70%)	15 (30%)	
Other chemotherapy	10 (83%)	2 (17%)	
Best response to immunotherapy			0.19
PR	5 (45%)	6 (55%)	
SD	17 (71%)	7 (29%)	
PD	35 (74%)	12 (26%)	
ECOG at salvage chemotherapy[a]			0.12
0	5 (45%)	6 (55%)	
1	33 (69%)	15 (31%)	
2-3	18 (82%)	4 (18%)	
Site of progression after immunotherapy			0.78
Locoregional	25 (74%)	9 (26%)	
Distant	17 (68%)	8 (32%)	
Both	15 (65%)	8 (35%)	

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, ECOG: Eastern Cooperative Oncology Group.
[a] One missing data for initial location and ECOG at salvage chemotherapy.

4. Discussion

We present herein the results of the first retrospective study which evaluated the response to SCT after failure of PD-1/PD-L1 alone or in combination in patients treated for R/M SCCHN. In our study, we observed a documented ORR to SCT of 30% (25/82) which is three to five times higher than the best ORR reported in second-line phase 2 or 3 trials in these patients [3–5]. This result is all the more remarkable because those patients were heavily pretreated (62 patients [76%] received SCT as third-line therapy or more).

Table 3
Prognostic analysis of OS and PFS after SCT: univariate analysis.

Patients	OS		PFS	
	Median (m)	Log rank p-value	Median (m)	Log rank *P*-value
Gender		0.95		0.72
Male	7.4		3.3	
Woman	8.2		3.7	
Age at progression after ICI		0.82		0.50
<60 years	8.0		4.9	
≥ 60 years	7.4		2.7	
Number of lines prior ICI		0.27		0.13
0-1	8.2		4.6	
≥2	4.8		2.9	
Type of CT prior ICI		0.02		0.008
None	12.3		5.3	
Platinum based	8.2		4.6	
Other CT	3.5		2.4	
Best response to ICI		0.003		0.015
PR	Not reached		5.8	
SD	9.9		5.0	
PD	5.0		2.6	
Site of progression after ICI		0.14		0.13
Locoregional	6.7		2.8	
Distant	10.2		5.1	
Both	6.7		4.4	
PS at SCT (n = 81)		<0.0001		0.002
ECOG 0-1	11.3		4.9	
ECOG 2-3	2.3		2.2	
Type of SCT		0.40		0.44
Cetuximab + taxane ± platinum	8.0		5.6	
Other	7.7		3.4	

OS: overall survival; PFS: progression-free survival; CT: computed tomography; ICI: immune checkpoint inhibitor; PD: progressive disease; SD: stable disease; PR: partial response; PS: performance status; SCT: salvage chemotherapy; ECOG: Eastern Cooperative Oncology Group.

Table 4
Prognostic analysis of OS and PFS after SCT: multivariate analysis.

Patients	HR	95% HR CI		*P*-value
a. PFS				
Type of CT prior ICI				**0.024**
Other CT	1			
Platinum based CT	0.460	0.232	0.913	
No prior CT	0.337	0.151	0.749	
Best response to ICI				**0.049**
PD	1			
SD	0.555	0.315	0.980	
PR	0.455	0.205	1.010	
PS at SCT				**0.030**
1	1			
2	1.837	1.061	3.183	
b. OS				
Type of CT prior ICI				**0.075**
Other CT	1			
Platinum based CT	0.445	0.204	0.969	
No prior CT	0.384	0.158	0.936	
Best response to ICI				**0.026**
PD	1			
SD	0.510	0.268	0.970	
PR	0.287	0.086	0.957	
PS at SCT				**<0.0001**
1	1			
2	4.581	2.381	8.814	

HR: hazard ratio; CI: confidence interval; CT: computed tomography; ICI: immune checkpoint inhibitor; PD: progressive disease; SD: stable disease; PR: partial response; PS: performance status; SCT: salvage chemotherapy.

These findings were consistent with initial data reported in the literature in advanced NSCLC. Leger *et al.* presented a response rate of 27% (18/67) to SCT in patients with advanced NSCLC who had progressed on ICI with an odds ratio of 0.30 for achieving partial response [14]. Similarly, Schvartsman *et al.* reported the MD Anderson Cancer Center data with a confirmed ORR of 29% (8/28) to single-agent chemotherapy in metastatic NSCLC after ICI failure with a median PFS of 4.7 months and median OS of 9.0 months [11]. More recently, Park *et al.* published a retrospective analysis of 73 patients who received SCT after progression on PD-1/PD-L1 inhibitors in advanced NSCLC. The ORR was 53.4% (39/73) which was statistically higher than ORR achieved with last chemotherapy before immunotherapy (34.9%, $P = 0.03$) and similar PFS with chemotherapy before and after checkpoint blockade [15]. Same findings were observed in cHL. Rossi *et al.* demonstrated an ORR of 67% (20/30) to SCT given alone or in combination with ICI in patients with cHL after failure to respond to PD-1 inhibitors given as monotherapy in a series from Lymphoma Study Association centres. In their report, 20% of patients (6/30) were amenable to allogenic stem cell transplantation after SCT [13]. It remains to be determined in which extent SCT contributes to the OS improvement reported with ICIs in several tumour types.

One of the hypotheses which may explain these findings is the chemosensitivity restoration due to the tumour microenvironment modification induced by immunotherapy. Indeed, several studies have described the immunosuppressive effects of cytotoxic chemotherapy which enhance immune activity against the tumour when given before immunotherapy [16]. Multiple chemotherapies induce immune-reactive effects such as upregulation of major histocompatibility complex molecules or tumour antigens presentation [17,18]. Moreover, chemotherapy has been shown to eliminate myeloid-derived suppressor cells/regulatory T-cells, increase helper T-cell accumulation and upregulate death receptor in tumour cells [19,20].

The outcomes reported in our study seem to be better than those reported with second-line treatment in patients with SCCHN suggesting that chemotherapy should be given in patients with R/M SCCHN who progressed on immunotherapy because the ORR to SCT is about 30% even in unfit patients. This high ORR can be an argument to stop ICI early after progression in

patients with SCCHN who presented altered performance status and/or high burden of disease after immunotherapy especially with the low incidence of pseudoprogression in SCCHN which does not exceed 10% and the risk of hyperprogressive disease reported in SCCHN which is about 29% [21,22].

Another hypothesis is that the enhanced response rate to SCT may be reflective of the effect of concurrent presence of chemotherapy and immunotherapy due to long antibody half-life. In our study, the median time between the last dose of ICI and the first dose of SCT was 1.0 months and the median PFS was 3.6 months which correspond to the duration of elimination of immunotherapy. In fact, the efficacy of the combination of chemotherapy and immunotherapy has been demonstrated through the KEYNOTE-048 trial. This phase III trial compared pembrolizumab or pembrolizumab and chemotherapy with the EXTREME regimen as first-line setting in R/M SCCHN. Pembrolizumab and chemotherapy arm was associated with a significant prolonged median OS (13.0 months) compared with the EXTREME arm (10.7 months; HR, 0.77; $P = 0.0034$) [23].

We suggest that checkpoint blockade may enhance the initial response to SCT but the immunomodulatory effects of this chemotherapy are likely not persistent. To test this hypothesis, we should continue immunotherapy while adding cytotoxic agents when the disease progresses on ICI. Rossi *et al.* reported an ORR of 86% (6/7) in patients with cHL in whom chemotherapy was added to PD-1/PD-L1 inhibitors after progression on these agents [13]. There is a phase II trial investigating this treatment strategy in patients with advanced NSCLC (NCT03083808).

The alternative explanation is that early progression under immunotherapy may have been followed by response regardless of any subsequent treatment. In fact, in the pivotal trial with nivolumab (CheckMate-141), 62 patients were treated beyond progression with at least one dose of nivolumab. The median OS of these patients was 12.7 months (95% CI: 9.7, 14.6) and 24% of patients presented a reduction in volume of target lesions but only 3 patients of 62 (5%) achieved partial response in this subgroup [24]. The ORR observed in this subgroup was lower than the 30% of response rate reported in our cohort. In addition, nivolumab was continued beyond progression in patients with no rapid disease progression, stable performance status and no delay of an imminent intervention to prevent serious complications of disease progression.

Our study had several limitations. First we reviewed retrospectively the data and medical records of patients treated with ICI and our criteria were not assessed prospectively. Second, all patients received immunotherapy in clinical trials which forbid the analysis of data concerning ICI. Third, chemotherapy regimens were heterogeneous and depended on the previous treatment given to the patient and the choice of physician. In addition, ICI administered were heterogeneous and were given as monotherapy or in combination.

In conclusion, our study is, to the best of our knowledge, the first one to show an increased response rate to chemotherapy (30%) administered after progression on ICI in patients with R/M SCCHN. These data support the hypothesis that immunotherapy enhances patient response to chemotherapy. Prospective clinical trials and large cohorts are needed to confirm the phenomenon and optimize the sequencing of multiple cytotoxic agents and immunotherapy drugs available in the treatment of R/M SCCHN.

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Conflict of interest statement

None declared.

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