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Nivolumab for recurrent or metastatic head and neck carcinoma: a retrospective and prospective real-life study

Sophie Bargas Bouttes

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Année : 2021

**Nivolumab en vie réelle dans le cadre des cancers des voies aérodigestives
supérieures en rechute ou métastatiques après sel de platine**

THÈSE
POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE
SPÉCIALITÉ : ONCOLOGIE MEDICALE

Par Mme Sophie BARGAS BOUTTES

[Données à caractère personnel]

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Abréviations

CPS: combined positive score

CTLA-4: cytotoxic T-lymphocyte associated protein 4

EBV: Epstein Bar virus

EGFR: epidermal growth factor receptor

FDA: food and drug administration

HBV, HCV: hepatitis B virus, hepatitis C virus

HIV: human immunodeficiency virus

HLA: human leucocyte antigen

HNSCC: head and neck squamous cell carcinoma

HPV: human papillomavirus

IL: interleukin

IrAEs: immune related adverse events

MDSCs: myeloid-derived suppressor cells

MRI: magnetic resonance imaging

NK cells: natural killer cells

NLR: neutrophil to lymphocyte ratio

OR: odds ratio

ORR: objective response rate

OS: overall survival

PD-1: programmed cell death protein 1

PDL-1: programmed death-ligand 1

PERCIST: PET Response Criteria in Solid Tumor

PET: positron emission tomography

PFS: progression free survival

PS: performance status

RECIST: Response Evaluation Criteria in Solid Tumor

TGF- β : transforming growth factor beta

TILs: tumor infiltrating lymphocytes

VEGF: vascular endothelial growth factor

Résumé

Contexte : La majorité des patients atteints d'un cancer des voies aérodigestives supérieures ont de nombreuses comorbidités liées à la consommation de tabac et d'alcool. Les essais cliniques ne sélectionnent qu'une partie de cette population fragile. L'utilisation du nivolumab dans les cas de cancers des voies aérodigestives supérieures en rechute ou métastatiques après une chimiothérapie par sel de platine est autorisée en France depuis janvier 2018. Une étude en vie réelle semble essentielle afin de confirmer l'efficacité et la tolérance du nivolumab pour l'ensemble des patients.

Méthodes : Dans cette étude bicentrique rétrospective et prospective, nous avons inclus les patients suivis pour un cancer des voies aérodigestives supérieures en rechute ou métastatiques après une chimiothérapie par sel de platine. Les patients ont été traités par nivolumab entre décembre 2017 et novembre 2020. L'objectif principal était le taux de réponse objective. Les objectifs secondaires étaient la survie globale, le temps médian jusqu'à progression, le profil de tolérance, l'identification de facteurs prédictifs de réponse et le temps médian jusqu'à progression de la ligne de chimiothérapie utilisée après échec du nivolumab.

Résultats : Quatre-vingt-quinze patients ont été inclus dans cette étude. Le taux de réponses objectives était de 22% dont 5 réponses complètes avec un temps médian jusqu'à progression de 3 mois. La médiane de survie globale était de 8 mois et le taux de survie à 1 an était de 38%. Un bon état général avec un performance status de 0 ou 1 (OR 7,11 ; 95% CI [1,53-33,05] ; $p = 0,012$), l'utilisation du cisplatine en 1ère ligne (OR 4,91 ; 95% CI [1,25-9,69] ; $p = 0,017$) et l'apparition d'effets secondaires sous immunothérapie (OR 10,59 ; 95% CI [2,30-48,73] ; $p = 0,001$) étaient significativement associés à une amélioration du taux de réponses objectives. Huit pour cent de toxicité de grade 3 ou 4 ont été décrites dont 3 décès attribuables au traitement : 2 pneumopathies auto-immunes et un rejet de greffe hépatique. Le temps médian jusqu'à progression du traitement utilisé après échec du nivolumab (taxanes, méthotrexate, sels de platine) était de 3 mois.

Conclusion : Le nivolumab est un traitement sûr et efficace dans les cas de cancers des voies aérodi-gestives supérieures y compris pour les patients fragiles non éligibles aux essais cliniques. L'apparition d'effets secondaires immunologiques et un état général conservé semblent associés à une amélioration du taux de réponse objective.

MOTS CLES : Nivolumab, inhibiteurs de points de contrôle immunitaires, cancers des voies aérodi-gestives supérieures en rechute ou métastatique, étude en vie réelle, facteurs prédictifs de réponse

Abstract

Background: Most of the patients with head and neck squamous cell carcinoma (HNSCC) present many comorbidities linked to consumption of tobacco and alcohol, making them a fragile population. Clinical trials' inclusion criteria select only a part of this population. Therefore, a real-life study seems essential to confirm the efficacy and safety of nivolumab for recurrent or metastatic HNSCC after platinum chemotherapy.

Methods: In this bicentric retrospective and prospective study, we included patients with a recurrent or metastatic HNSCC in progression after a platinum chemotherapy treated by nivolumab from December 2017 to November 2020. The primary end point was the objective response rate. The secondary end points were overall survival (OS), progression free survival (PFS), safety, identification of response's predictive factors and median time until progression of chemotherapy after nivolumab exposure.

Results: Ninety-five patients were included. Overall response rate was 22% including 5 complete responses with a PFS of 3 months. OS was 8 months and the 1-year survival rate was 38%. Performance status of 0 or 1 (OR 7,11; 95% CI [1,53-33,05]; $p = 0,012$), cisplatin use in first line protocol (OR 4,91; 95% CI [1,25-9,69]; $p = 0,017$) and immune adverse events (OR 10,59; 95% CI [2,30-48,73]; $p = 0,001$) were significantly associated with a better response rate. Nivolumab appeared to be safe, with 8% of grade 3 or 4 immune adverse events. Three treatment related deaths were reported: two pneumonitis and one liver graft rejection. Patients treated by chemotherapy (taxanes, methotrexate or platin) after nivolumab had a median time until progression of 3 months.

Conclusion: Nivolumab is a safe and efficient treatment after platinum exposure for recurrent or metastatic HNSCC patients, whatever their condition. However, a good general condition and immune adverse events are associated to a better response rate.

KEYWORDS: Nivolumab, Immune checkpoint inhibitors, recurrent or metastatic head and neck cancers, real-life study, predictive factors of response

Nivolumab for recurrent or metastatic head and neck carcinoma: a retrospective and prospective real-life study

Introduction

The head and neck squamous cell carcinoma (HNSCC) is a heterogeneous group of tumors including oropharynx, oral cavity, hypopharynx, nasopharynx and larynx cancers.

The global burden of cancer estimated 834 860 new HNSCC worldwide in 2018 representing 4.9% of all cancers except non melanoma skin cancers. The deaths attributable to HNSCC were 431 131 representing 4.5% of cancer deaths.¹

The past three years were marked by a change in epidemiology with an oropharyngeal, hypopharyngeal and oral cavity cancers increase due to the rising of human papillomavirus (HPV) related tumor and a decrease incidence rate of larynx cancer. Tobacco and alcohol are essentially linked with laryngeal cancer.² Their concomitant consumption has a synergistic effect with relative risk of 35 to develop HNSCC.³ HPV chronic infection (mostly HPV 16) is mostly linked with oropharyngeal cancers whereas Epstein Bar virus (EBV) infections is associated with nasopharynx tumors. Most of the patients present comorbidities mainly cardiovascular problems, induced by tobacco consumption. Moreover, the exposition of alcohol and tobacco induces a high risk of developing metachronous or synchronous cancer.³

We can distinguish 2 entities of HNSCC according to HPV status defined by different tumoral evolution and prognosis. HPV positive HNSCC occurs in younger patients without tobacco use and have better prognosis because of radio and chemosensitivity.⁴ The HPV negative HNSCC concerns former or current smoking patients with frequently a mutation of tumor suppressor gene TP53.²

Despite combinations of radiotherapy, chemotherapy and surgery, HNSCC prognosis is poor. After radiotherapy, 24% of locally advanced HNSCC patients will experience a recurrence.⁵

The median overall survival in case of recurrent or metastatic disease treated with a platinum-based doublet chemotherapy and cetuximab (EXTREME protocol) is 10 to 14.5 months.^{6,7} In case of platinum

failure, second line chemotherapy options are very restricted based on taxanes or methotrexate and have a low efficiency with median overall survival of 3 to 5 months.^{8, 9, 10}

HNSCC is an immunosuppressive disease associated with an immune escape caused by several mechanisms. First of all, the human leucocyte antigen (HLA) class I expression is altered via mutations resulting in a decrease of tumor antigenic peptides presentation to T lymphocytes.¹¹ Secondly, tumor cells express immune checkpoint molecules inhibiting immune cell inflammatory activity like the program death protein-1 (PDL-1). PDL-1 is the ligand of programmed cell death protein 1 (PD-1) expressed on T lymphocytes and induces a loss of cytotoxic activity function. Moreover, tumor cells produce immunosuppressive cytokines like interleukins IL-6, IL-10 and transforming growth factor beta (TGF- β) which inhibit activation of natural killer cells (NK cells) and T lymphocytes and stimulate regulatory T cells.¹²

The last ten years have been marked by the development of immune checkpoint inhibitors targeting PD-1, PDL-1 or cytotoxic T-lymphocyte associated protein 4 (CTLA-4). They restore the ability of immune cells to target and kill tumor cells and avoid their immunosuppressive state.¹³ Immune checkpoint inhibitors are used in several cancers as melanoma, lung cancers or renal cell carcinoma.^{14, 15, 16}

Nivolumab is a human monoclonal IgG4 immunoglobulin, targeting the PDL-1, improving the overall survival (OS) from 2,4 months compared to standard chemotherapy (docetaxel, cetuximab or methotrexate) and significantly reducing the risk of death by 30% in case of recurrent or metastatic HNSCC platinum refractory based on CheckMate 141 results.¹⁰ Response rate of this anti PD-1 was 13,3%. The US food and drug administration (FDA) approved its use in case of recurrent or metastatic HNSCC platinum refractory in 2016. In France, it is available since January 2018. Nevertheless, the trials population is not completely representative of real life and patients with a poor performance status (PS) were excluded from CheckMate 141.

Thirty-six percent of the CheckMate 141 population were alive after 12 months, but some patients appeared to benefit more from chemotherapy during the first 3 months as illustrated by an initial cross over of overall survival curves.¹⁰ Thus, it's essential to identify predictive biomarkers of response. In the literature, some potential predictors of response are described as PDL-1 expression, tumor

mutational burden, tumoral microenvironment composition, HPV status and host's microbiome.¹⁷ The tumor microenvironment is a complex structure composed of tumor cells, immune cells, fibroblasts, and endothelial cells. The HNSCC are highly infiltrated by immune cells whose composition varies according to tobacco consumption, HPV status and anatomical site. The type and levels of tumor infiltrating lymphocytes (TILs) is associated with a good prognosis and can be a good predicting response factor. Regulatory T lymphocytes, M2 macrophages, neutrophils, dendritic cells and myeloid-derived suppressor cells (MDSCs) are immunosuppressive cells and are associated with a poor prognosis. A high concentration of CD8 cytotoxic lymphocytes and NK cells improve survival through their anti-tumour cytotoxic activity.¹⁸

The aim of this observational study was to evaluate efficacy, safety and identification of predictive factors of response to nivolumab in recurrent or metastatic HNSCC in real world.

Methods

Patients

We selected all patients aged over 18 years, who had received at least one cure of nivolumab in a context of a locally advanced or metastatic HNSCC, histologically confirmed. All cases had been treated by platinum chemotherapy as adjuvant therapy or in a context of recurrent or metastatic disease. Carboplatin or cisplatin could have been used. Patients were not suitable for local treatment. All performance status (PS) scores were included. Patients with an autoimmune disease, a human immunodeficiency virus (HIV) or hepatitis B or C virus (HBV, HCV) infection weren't excluded. All administration protocols were accepted, nivolumab was administered at a dose of 3mg per kilogram or 240mg every 2 weeks or 480mg every 4 weeks. To compare our results, a course of nivolumab was defined to 4 weeks (J1=J28).

Study design

This is a retrospective and prospective observational study conducted at University Hospital of Grenoble and Annecy's Hospital. Retrospective part concerned all patients treated before November 2019. The

inclusion for the prospective part was executed between November 2019 to November 2020. The follow up period was from December 2017 to April 2021.

The primary end point was objective response rate (ORR) defined as proportion of patients with a complete or partial response according to the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 evaluation or PET Response Criteria in Solid Tumor (PERCIST).

Secondary end points were overall survival (OS), progression free survival (PFS), identification of response predictive factors, safety and time until progression of chemotherapy after nivolumab exposure. OS was defined as the period from the first nivolumab injection to the date of death to any cause. PFS was defined as the period from the first nivolumab administration to the date of progression disease diagnosis or death. The response predictive factors evaluated were antibiotics or corticosteroid consumption during the 4 weeks before the first nivolumab administration; malnutrition, lymphopenia, neutrophil to lymphocyte ratio (NLR), metastatic disease and PS of 0 or 1 at the first injection; history of lymph node dissection, cetuximab used, cisplatin first line treatment; age over 75 years and immune adverse events.

Malnutrition was defined by a seric albumin under 30g/l. Lymphopenia was defined as a lymphocyte count under 1G/l. NLR was defined as high if it was greater than or equal to 5.

Tumor assessments were performed according to each center habits either generally at baseline and every 3 months by computed tomography, magnetic resonance imaging (MRI) or positron emission tomography (PET).

Clinical and biological adverse effects were assessed after each nivolumab injection. Adverse events were classified according to the Common Terminology Criteria for Adverse Events version 4.0.

Data were collected from patient files and were recorded anonymously. All the data collected were: age; gender; tobacco and alcohol consumptions; auto-immune disease; HIV, HBV and HCV status; PS; primary tumor localization; TNM classification at diagnosis; p16 status; PDL-1 rate; first line treatment; cisplatin or carboplatin use; head and neck radiotherapy or surgery antecedent, number of prior treatments before nivolumab introduction; weight to the first and last administration; feeding gastrostomy; tracheostomy; locally advanced or metastatic status; localization of metastases; antibiotic and corticosteroid use during the 4 weeks before nivolumab introduction; leukocytes, neutrophils,

lymphocytes count to the first, second and third nivolumab injection; seric albumin at the beginning of immunotherapy; first and second radiologic and clinical evaluation; date of first and last nivolumab administration, number of immunotherapy courses; adverse events related to nivolumab; use of corticosteroid to manage toxicity; treatment administration schedule; reason for nivolumab interruption; chemotherapy used after immunotherapy failure and its duration of administration; date of death. A non-opposition information letter was given to patients. Our study was recorded to the Clinical Research and Innovation Department of the University Hospital of Grenoble.

Statistical Analysis

The overall survival was estimated by the Kaplan-Meier method. To assess the association between predictor factors and objective response rate, univariate analyses were conducted. Subgroup analyses were determined by Chi2 test. In case of theoretical population size less than 5, Fisher's exact test was used. The Odds ratio (OR) were estimated by logistic regression models. $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using R4Web software.

Results

Patient characteristics

From July 2019 to November 2020, we enrolled 95 patients whose median age was 66 years. They were mostly tobacco users (87%) and alcoholic consumers (69%). They were mainly treated for oropharyngeal (42%) or hypopharyngeal cancer (21%). Patient's characteristics are summarized in **Table 1**. The entire population received a first-line platinum regimen via the EXTREME protocol, chemoradiation or other chemotherapy with platinum. Carboplatin was used in case of poor performance status, cisplatin contraindication or elderly patients.

Tumor p16 status was reported for 48 patients (50%) and 6 of them (12%) had positive p16 status. PDL1 status was investigated for 7 patients. Fifty patients (53%) had a loco-regional relapse and 45 patients

(47%) had a metastatic form mainly pulmonary (84%). Nivolumab was essentially used as second line systemic therapy (73%).

Efficacy

ORR was 22% including 5 complete responses (5%) and 16 partial responses (17%). Seven patients (7%) had a stable disease. (**Table 2**) Of the 95 patients, 3 (3%) were still being treated with nivolumab at the time of analysis. Six patients (6%) have interrupted their treatment after 2 years in a context of complete response for 5 of them and a prolonged stability for the other. Eleven patients (12%) continued nivolumab despite a progression of the disease on the first radiologic evaluation because of clinical benefit but only 2 had a stable disease on the second evaluation. Eight patients (8%) experimented a quick progression of the disease just after the immunotherapy's start defined by decline of the general condition and a higher tumor burden. On these 8 patients, 7 (88%) had a loco-regional disease. This hyperprogressor population had a median OS of 1,5 month [1-10] and a PFS of 0,5 month. Four (50%) of them died before testing another chemotherapy treatment.

A median of 3 nivolumab injections have been administered. Overall median PFS was 3 months [0-41]. Median OS was 8 months [0,5-41] with a 1-year survival rate from 38% (36 patients). (**Figure 1**) Seventy-one patients (75%) died with the main cause of death being disease progression. Responders had a median OS of 19 months [5-41] and a median PFS of 17 months [3-41].

In the subgroup analysis, 3 predictor factors significantly associated with an objective response were identified. Eighteen patients (19%) in good general condition with a PS of 0 or 1 had an objective response versus 2 (2%) with a PS of 2 or more (**OR 7,11; 95% CI [1,53-33,05]; $p = 0,012$**). Fourteen patients (15%) previously treated with cisplatin in first line protocol were responders versus 7 (7%) treated with carboplatin (**OR 4,91; 95% CI [1,25-9,69]; $p = 0,017$**). Nineteen patients (20%) with immune adverse events were responders versus 2 patients (2%) (**OR 10,59; 95% CI [2,30-48,73]; $p = 0,001$**).

Fifty-six patients (59%) received a new line of chemotherapy following immunotherapy's progression. Median time until progression to single agent chemotherapy after nivolumab failure was 3 months.

Taxanes were mainly used (64%) then platinum regimen (25%) and methotrexate (7%). The median time until progression to taxanes was 3,75 months [0-10], 5,5 months [0-14] for platin based protocols and 2,25 months [0-3] for methotrexate.

Safety

Immune related adverse events (irAEs) are summarized in **Table 3**. Sixty percent of the patients experimented an adverse effect mainly grade 1. The most frequent of any grade were hypothyroidism, diarrhea, skin toxicity as pruritus, arthralgia, and myalgia. Eighteen patients (19%) received L-thyroxin treatment for hypothyroidism. Dysthyroid could occur even after nivolumab discontinuation. One case of hypothyroidism was diagnosed 4 months after the last injection of nivolumab. One hypophysitis occurred after 17 months of treatment. Seven patients (7%) experimented a grade 3 or 4 toxicity: pneumonitis, hepatitis, diarrhea, and ulcerative colitis. One patient has presented a demyelinating sensory neuropathy like Guillain-Barre syndrome with no severity. Three treatment related deaths (3%) were reported: two pneumonitis and one liver graft rejection. One patient had a dose interruption for hepatitis and seven patients discontinued nivolumab due to treatment-related adverse event. One patient which interrupted nivolumab injection in the first place in a context of hepatic cytolysis received a rechallenge without recurrent of hepatic toxicity. Corticosteroid was used for 14 patients (15%) to manage toxicity: 79% systemic corticosteroid therapy and 21% topical corticosteroid for skin toxicity. Infliximab was successfully used in a context of ulcerative colitis resistant to corticosteroid. Furthermore, thymoglobulin was not effective for a liver transplant rejection. Chronical viral infections of hepatitis B or C were not associated with more hepatic toxicity.

Discussion

Despite elderly patients (median age: 66 years vs 59 years) with a worse general condition (PS over 2: 34% vs 0,4%) compared to the CheckMate 141 study, the objective response rate was better 22% vs 13,3%.¹⁰ Our objective response rate was better than 2 retrospective cohorts (15,7% and 13,5%) and the

prospective French trial TOPNIVO (16%).^{19, 20, 21} This difference can be explained by radiological evaluations diversity: CT-scan, MRI or PET scan. Moreover, tumor assessments were mainly realized every 3 months while evaluations were done every 6 weeks in CheckMate 141.¹⁰ Nevertheless, the analysis were not conducted by an independent centralize committee of radiologists and RECIST score weren't always available on the radiologist reports. Finally, pharyngeal tumors were associated to a better response rate than oral cavity cancers in Hanai and al. trial.²⁰ Our population consisted of more pharynx cancers and less oral cavity tumors than CheckMate 141 trial with respectively 63% vs 38% and 14% vs 45%.¹⁰ All these elements may have contributed to an overestimation of the ORR. The median PFS was comparable 3 months vs 2 months.¹⁰ Median OS was similar 8 months vs 7,6 months.¹⁰ Nivolumab can induce prolonged responses in melanoma, lung cancer and renal cell carcinoma.^{14, 15, 16} Fourteen of our patients (15%) had a response for more than 12 months suggesting that prolonged responses can be also occurring in HNSCC.

Some patients might present a drastic acceleration of tumoral growth rate shortly after the immunotherapy's start resulting in a crossover between the arm of immunotherapy and chemotherapy overall survivals called hyperprogression.^{22, 23, 24} However, there is no standardization of the definition which varies accross studies with 3 different algorithms.^{23, 25} Saada and al. identified an hyperprogression rate of 29% in HNSCC retrospective study whose principal risk factor was regional recurrence.²⁶ In our study, 8 patients (8%) presented an impressive rapid increase of tumoral burden with deterioration of general condition (asthenia and weight loss). Seven (88%) had a loco-regional disease but this association wasn't significative ($p = 0,06$). These patients had a median OS of 1,5 months. Nevertheless, none of the 3 known definitions could be used due to the lack of systematic determination of the tumor growth rate before the introduction of immunotherapy.

Despite radiological progression, nivolumab could be used if the patients present clinical improvement, stable PS, absence of rapid progression and good tolerance.²⁴ In a post hoc analysis of CheckMate 141, 3 patients (1,3%) experimented an objective response beyond the first radiological progression.²⁷ This atypical response is called pseudo-progression due to tumoral immune infiltration.²³ In our study, no case of response after initial progression was described.

The sub-groups analysis identified 3 response predictor factors: PS of 0 or 1, cisplatin first line used and nivolumab IrAEs. This result about cisplatin could be biased because it is preferentially used in patients with good health conditions whereas carboplatin is preferred for unfit patients. PS of 0 or 1 was associated to better response rate like the real-life retrospective study of Hanai.²⁰ Good general conditions may be associated with a less aggressive disease and therefore a better prognosis. In the literature, the occurrence irAEs is associated with better OS and PFS, regardless of severity grade.^{19, 28} These symptoms usually associated with an increase inflammatory activity.²⁹ These subgroup results were not validated by multivariate analysis because of limited population size.

None of patients over the age of 75 responded to nivolumab but 8 of them (67%) had a poor PS over 2. This difference was not significant. This result could be explained because this population was limited to only 12 patients.

The HNSCC is characterized by an epidermal growth factor receptor (EGFR) overexpression which modulate PDL-1 expression. It appears that cetuximab can downregulate PDL-1 expression.³⁰ In our study, prior cetuximab use didn't modify the efficacy of nivolumab which is consistent with previous findings.³¹

A comparative study of the p16 status wasn't conducted because the p16 positive population was very restricted and the p16 status was missing for half of the patients. The systematical screening of p16 overexpression in oropharyngeal cancer was not performed for diagnosis before 2016.

The immune cell infiltration within the tumor microenvironment plays a central role in tumor development. Neutrophils secrete several proteases (elastases, cathepsin G and proteinase 3) which activate matrix metalloproteinase degrading extracellular matrix and promoting tumor invasion.³² Moreover, degranulation of tumor infiltrating neutrophils increase vascular permeability and promotes angiogenesis via vascular endothelial growth factor (VEGF) secretion.³³ Several studies have found an association with a high NLR before immunotherapy introduction and poor prognosis in various

malignancies.³⁴ Ueda and al. found a significantly association in HNSCC between NLR higher than 5 before the initiation of immunotherapy and worse overall survival (HR 6,20; $p = 0,028$).³⁵ The NLR increases in patients who experienced disease progression.³⁶ In our study, we couldn't find a significantly association of the neutrophil to lymphocyte ratio (NLR) higher than 5 and poor ORR. Lymphopenia under 1G/l wasn't a predictive factor of response in our study. Nevertheless, Ho and al. described a significant lower PFS in case of lymphocytes count under 0,6 G/l before the initiation of immunotherapy. (60 vs 141 days, $p < 0,05$).³⁷

Exposure to antibiotics within month before start of the immune checkpoint inhibitors therapy is associated with decreasing survival and ORR by inducing gut dysbiosis.^{38, 39} Baseline corticosteroids use (prednisone ≥ 10 mg/day) is significant associated with decreased OS and PFS in non-small cell lung cancer given their immunosuppressive properties.⁴⁰ We were not able to come to this finding in our own study. These results could be explained by the fact that some patients could have been prescribed antibiotics by their GPs without our knowledge and by a limited power due to patients' small number.

The actual predictive biomarkers present poor sensitivity and their use in the clinic is still complicated. Anti PDL-1 therapy is complex because some patients display general improvement after nivolumab treatment despite the absence of PDL1 overexpression in the tumor.¹⁰ But we must stay aware that PDL-1 expression is evolving from cancer to another and because of tumor heterogeneity; the evaluation of the expression can also be influenced by the multitude of antibodies available. In the end, the best strategy would probably rely on the development of a predictive score based on more parameters: histology, PS, composition of TILS, stage cancer, ...

Three nivolumab administration modalities were accepted in our cohort. The French authorities recommend the protocol at 240mg every 2 weeks, but our study highlighted differences in prescription habits between 3mg/kg or 240mg protocol depending on centers. Moreover, in the context of the sanitary crisis of COVID 19, 19 patients (20%) were treated with 480mg of nivolumab each 4 weeks in order to

limit their venues to the hospital. There was no difference in term of efficacy and toxicity between the 2 administration's modalities.

IrAEs grades were quite comparable with the CheckMate 141 (60% vs 58,9%) except for grade 3 or 4 toxicities which were present in 7% of patient in our study vs 13,1%. Two of these serious toxicities concerned patients with autoimmune diseases: one hypothyroidism and one ulcerative colitis. Patients with previous dysthyroidism had mainly an imbalance of thyroid-stimulating hormone level. CTLA-4 and PD-1 are involved in the tolerance mechanisms; therefore solid organ transplant patients are usually excluded from any immunotherapy' trial. Organ rejection occurred in 41% of grafted patients treated by immune checkpoint inhibitors with a median time of rejection from 21 days. In a cohort of Abdel-Wahab, graft loss was occurred in 81% complicated by 46% of deaths.⁴¹ Nivolumab present the highest graft rejection rate (52,2%) in a systematic review by Fisher and al.⁴² Two of our patients had a liver transplant and one of them suffered fatal liver rejection after 2 courses of nivolumab used as a rescue treatment. In conclusion, nivolumab must be used with caution in case of solid organ transplant after a multidisciplinary validation.

We didn't find viral reactivations or increased liver toxicity in case of hepatitis B and C as the CheckMate 040 results.⁴³

Recent data suggest better responses to chemotherapies following immune checkpoints inhibitors exposure especially in non-small cell lung cancers.⁴⁴ Two studies demonstrated higher PFS (3,6 and 4,24 months) with salvage chemotherapy after immunotherapy failure than standard second line chemotherapy (2,3 months).^{45, 46, 10}. This can be explained by a chemosensitivity restoration induced by modification of tumoral microenvironment. Moreover, the long nivolumab half time may result in the concomitant presence of chemotherapy and immunotherapy. In our study, the median time until progression was lower (3 months) but most of our patients received these chemotherapies as third line.^{45, 46} PFS for each chemotherapy regimens were quite comparable with second line standards: 3,75 months for taxanes vs 1,7 to 6,2 months; 5,5 months for platinum combination vs 1,7 to 6,5 months and 2,25 months vs 1,5 to 1,9 months for methotrexate.⁹

THÈSE SOUTENUE PAR : Sophie BARGAS BOUTTES

TITRE :

NIVOLUMAB EN VIE REELLE DANS LE CADRE DES CANCERS DES VOIES AERODIGESTIVES SUPERIEURES EN RECHUTE OU METASTATIQUE APRES SEL DE PLATINE

Conclusion:



Nivolumab is safe and efficient after platinum chemotherapy for recurrent or metastatic HNSCC. Despite an elderly population with poorer general conditions than CheckMate 141 patients, the objective response rate was 22%. Unfortunately, some patients did not benefit from immunotherapy especially with some cases of hyperprogression. Good general condition with a performance status of 0 or 1, first line cisplatin use and immune adverse events were significantly associated with a better objective response rate. Furthermore, the overall survival remained low with a median of 8 months. The publication of TOPNIVO trial results, a randomized French phase III are pending to confirm all these findings.

Nivolumab use is reassessed since the authorization of immune checkpoint inhibitors in first line for locally advanced or metastatic HNSCC. Lately, pembrolizumab has become the new first line gold standard, alone or associated with chemotherapy (platinum and 5FU) based on KEYNOTE 048 for HNSCC patients with a combined positive score (CPS) ≥ 1 .⁴⁷ That would restrict nivolumab utilization to relapses after EXTREME or TPEX chemotherapy regimen in case of negative CPS.^{48, 49}

VU ET PERMIS D'IMPRIMER

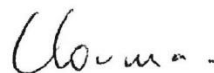
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Le Doyen de l'UFR de Médecine
Pr. Patrice MORAND


Pr. Patrice MORAND

LE PRESIDENT DE LA THESE



Pr. Mireille MOUSSEAU

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Annexes

Table 1. Characteristics of patients at baseline

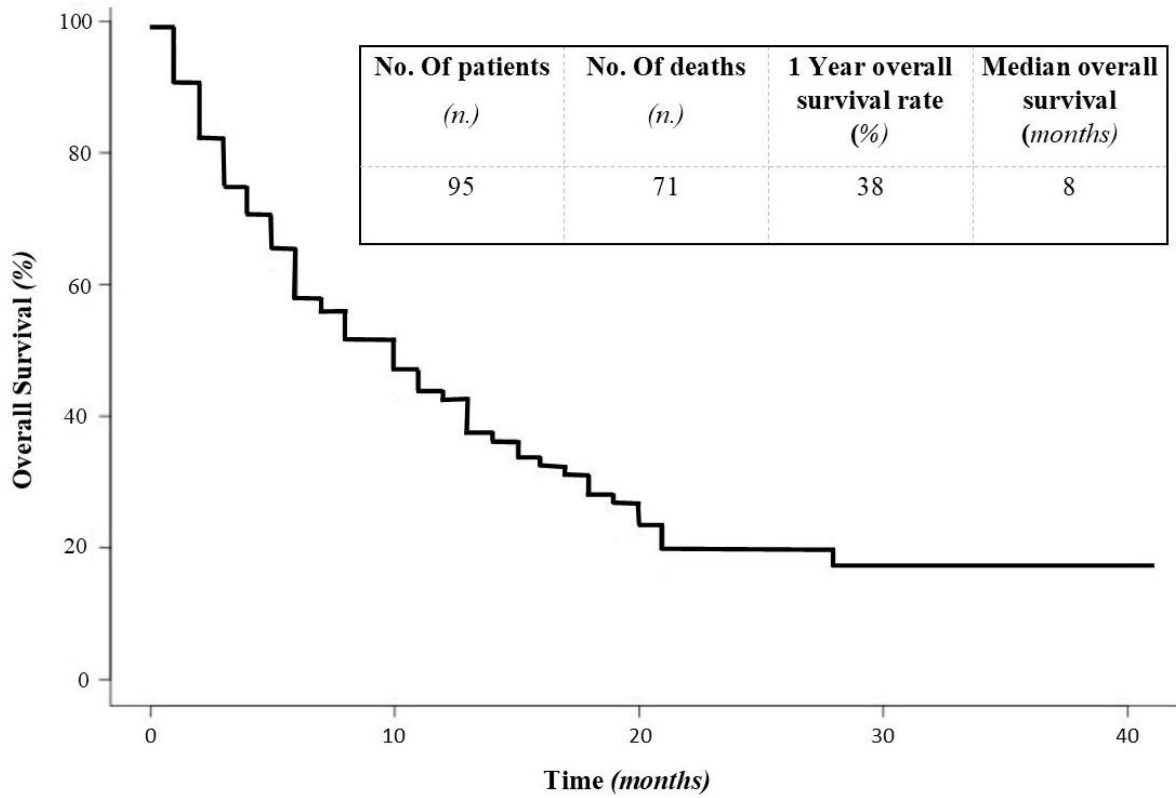
Characteristic	Nivolumab (95)
Age, years	
Median (<i>range</i>)	66 [44-82]
≥75 years (%)	12 (13%)
Sex <i>n.</i> (%)	
Male	78 (82%)
Female	17 (18%)
Smoking or tobacco use <i>n.</i> (%)	
Current or former	83 (87%)
Never	12 (13%)
Alcohol consumption <i>n.</i> (%)	
Current or former	65 (69%)
Never	30 (31%)
Autoimmune disease <i>n.</i> (%)	
Dysthyroidism	13 (14%)
Organ transplant	2 (2%)
Ulcerative colitis	1 (1%)
None	79 (83%)
Chronical infection disease <i>n.</i> (%)	
Hepatitis B	3 (3%)
Hepatitis C	2 (2%)
HIV	0 (0%)
None	57 (60%)
Not reported	33 (34%)
ECOG Performance Status score <i>n.</i> (%)	
0	8 (8%)
1	48 (51%)
≥2	32 (34%)
Not reported	7 (7%)
Site of primary tumor <i>n.</i> (%)	
Larynx	12 (13%)
Oral cavity	13 (14%)
Oropharynx	40 (42%)
Hypopharynx	20 (21%)
Others	10 (10%)
p16 status <i>n.</i> (%)	
Positive	6 (6%)
Negative	42 (44%)
Not reported	47 (50%)
PDL-1 expression level <i>n.</i> (%)	
<1	5 (5%)
≥1	2 (2%)
Not reported	88 (93%)

Number of previous systemic therapy regimen <i>n. (%)</i>	
1	69 (73%)
2	23 (24%)
≥3	3 (3%)
First line treatment <i>n. (%)</i>	
Radiotherapy and chemotherapy concomitant	30 (32%)
EXTREME protocol	33 (35%)
Others protocols	32 (33%)
Platinum used <i>n. (%)</i>	
Cisplatin	54 (57%)
Carboplatin	41 (43%)
Cetuximab used	
Maintenance therapy <i>n. (%)</i>	36 (38%)
Median cycles (<i>range</i>)	7 [1-45]
Radiotherapy <i>n. (%)</i>	80 (84%)
Chirurgical procedure <i>n. (%)</i>	54 (57%)
Lymph node dissection	48 (89%)
Stage of cancer <i>n. (%)</i>	
Loco-regional recurrence	50 (53%)
Metastatic	45 (47%)
Localization of metastases	
Lung	38 (84%)
Liver	6 (13%)
Bone	7 (15%)
Skin	4 (9%)
Others	8 (18%)
Corticosteroids within 4 weeks before nivolumab <i>n. (%)</i>	13 (14%)
Antibiotic within 4 weeks before nivolumab <i>n. (%)</i>	44 (46%)
Blood test for the first injection <i>n. (%)</i>	
Leucocytes < 4 G/l	11 (16%)
Neutrophils < 1.5 G/l	4 (4%)
Lymphocytes < 1 G/l	45 (47%)
Neutrophils/Lymphocytes < 5	49 (52%)
Albumin < 30 g/l	33 (35%)

Table 2. Response rate

Response Disease	n. (%)
Objective Response	21 (22%)
Complete Response	5 (5%)
Partial Response	16 (17%)
Stable disease	7 (7%)
Progression disease	67 (71%)
“Hyperprogression” disease	8 (8%)

Figure 1. Overall Survival



Months	0	3	6	9	12	15	18	25	30
Nivolumab	95	74	61	47	36	26	22	9	4

Table 3. Subgroup analysis

Predictive factors	Response Disease <i>n.</i>	No response disease <i>n.</i>	Univariate analysis <i>p</i>	Odds Ratio [Interval confidence 95%]
Lymph node dissection	10	38	0,956	0,861 [0,326-2,272]
Cisplatin first line treatment	14	27	0,017	4,91 [1,25-9,69]
Cetuximab maintenance	8	28	1	1,011 [0,373-2,743]
Metastatic disease	10	35	1	1,013 [0,384-2,673]
Antibiotic used in 4 weeks	8	36	0,684	0,707 [0,254-1,966]
Corticosteroid used in 4 weeks	1	13	0,179	0,231 [0,028-1,883]
NLR \geq 5	10	28	0,695	1,393 [0,511-3,794]
Lymphopenia (<1G/l)	11	34	0,89	1,222 [0,449-3,326]
Serum albumin <30g/l	2	11	1	0,709 [0,135-3,726]
Performance status 0-1	18	38	0,012	7,105 [1,527-33,054]
Age over 75 years	0	12	0,062	0 [0-NA]
Immune adverse events	19	35	0,001	10,586 [2,299-48,731]

Table 4. Immune treatment related adverse events

Events	Any grade n. (%)	Grade 3-4 n. (%)
Any event	86	7 (7%)
Nausea	8 (8%)	0
Diarrhea	13 (14%)	3 (3%)
Hypothyroidism	25 (26%)	0
Hyperthyroidism	5 (5%)	0
Hypophysitis	1 (1%)	0
Rash or Pruritus	13 (14%)	0
Pneumonitis	4 (4%)	2 (2%)
Liver disorder	3 (3%)	2 (2%)
Myalgia or Arthralgia	12 (13%)	0
Neurologic disorder	1 (1%)	0
Nephritis	1 (1%)	0

Le serment d'Hippocrate

Texte revu par l'Ordre des médecins en 2012

“ Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

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