Combination of radiation therapy-immunotherapy for head and neck cancers: Promises kept?

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Abstract

Chemoradiotherapy with concurrent cisplatin has been the standard treatment for locally advanced head and neck squamous cell carcinoma (HNSCC) for over 20 years. Recently, immunotherapy, a new therapeutic class, has emerged for patients with recurrent or metastatic HNSCC and has significantly extended their survival. Will it bring the same benefit to patients with localized tumors? There is a strong rationale for combining radiation therapy and checkpoint inhibitors for HNSCC. Indeed, radiation therapy can have both immunostimulatory and immunomodulatory effects. This is what explains the famous abscopal effect. The aim of this review is to present the data available on the combination of radiation therapy and immunotherapy for HNSCC.

Keywords: head and neck cancer; squamous cell carcinoma; radiotherapy; chemoradiotherapy; cisplatin; immunotherapy; immune checkpoint inhibitors; PDL1, PD1; abscopal effect.

Résumé

La chimioradiothérapie avec cisplatine est le traitement de référence des carcinomes épidermoïdes des voies aéro-digestives supérieures (VADS) localement avancés depuis plus de 20 ans. Récemment, l'immunothérapie, une nouvelle classe thérapeutique, a émergé pour les patients ayant des cancers des VADS en rechute ou métastatique et permis d'allonger significativement leur survie. Apportera-t-elle le même bénéfice aux patients avec des tumeurs localisées? Il existe un rationnel solide pour combiner radiothérapie et inhibiteurs de checkpoints pour les cancers des VADS. En effet, la radiothérapie peut avoir des effets immunostimulateurs comme immunomodulateurs. C'est notamment ce qui explique le fameux effet abscopal. Le but de cette revue est de faire le point sur les données disponibles sur l'association radiothérapie et immunothérapie pour les cancers des VADS.

Mots-clés : cancers ORL; cancers des voies aéro-digestives supérieures; carcinome épidermoïde; radiothérapie; chimioraiothérapie; cisplatine; immunothérapie; inhibiteurs de checkpoint; PDL1, PD1; effet abscopal.

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is the 6th leading cancer worldwide with 705,781 new cases and 358,140 deaths reported in 2018 (1). In France, 16853 new cases of HNSCC have been diagnosed in 2018, responsible for 4772 deaths (2).Most patients present with a locally advanced tumor at diagnosis. The risk of extension is mainly locoregional with only 10% to 20% of patients presenting with distant metastasis. Therapeutic management combines surgery, radiation therapy (RT), and chemotherapy based on the conclusions of a multidisciplinary tumor board. For locally advanced tumors (stages III and IV), standard treatment has been chemoradiotherapy (CRT) with concurrent cisplatin since the publication of the results of MACH-NC meta-analysis by J.P. Pignon et al (3,4). In a recent update on 107 randomized trials and 19,805 patients, concurrent chemotherapy significantly increased the rate of 5-year overall survival (OS) with an absolute benefit of 6.5% (HR=0.83; 95%CI 0.79; 0.86; p<0.0001) (5). For many years, researchers have tried to improve the efficacy of RT in order to cure more patients. Concurrent chemotherapy, by increasing tumor's radiosensitivity, is currently the most used. But other options are available such as hyperfractionation or combination with cetuximab, an EGFR inhibitor (6,7). A new way to explore is the combination of RT with immune checkpoint inhibitors. Indeed, these new drugs are more efficient than classical chemotherapy to treat patients with recurrent and/or metastatic HNSCC (8). The aim of this review is assess the potential benefit of these new combinations for locally advanced HNSCC based on the available data.

2. Rational of radiation therapy and immunotherapy combination for HNSCC

The immune system plays a dual role in cancer development: it can not only suppress tumor growth by destroying cancer cells or inhibiting their growth but also promote tumor

progression either by selecting for tumor cells that are more fit to survive in an immunocompetent host or by establishing conditions within the tumor microenvironment that facilitate tumor outgrowth. Schreiber et al have called this phenomenon "cancer immunoediting" (9). The goal of immunotherapy is to tip the scales in the right direction, towards tumor cells elimination rather than promotion. PD-1 (programmed cell death 1) is a protein found on the surface of T cells and is a component of the PD-1 / programmed death-ligand 1 (PD-L1) immune checkpoint. T cells can interact via PD-1 with a tumor cell presenting PD-L1 on its surface. This interaction inactivates the T cell and therefore inactivates one of the defense mechanisms of the immune system against tumor cells. Therefore, the PD-1 / PD-L1 complex plays a central role in the immune system. Immune checkpoint inhibitors are antibodies able to binding to PD-1 or PD-L1 and blocking them. Blocking the immune checkpoint by preventing the interaction between PD-1 and PD-L1 activates the immune system (10).

For lung cancer, immune checkpoint inhibitors were more efficient in patients with a higher number of somatic tumor mutations than those who had fewer (11). Tumor mutational burden (TMB) is now a well known a genomic biomarker that predicts favorable responses to immune checkpoint inhibitors (12). TMB in HNSCC is also quite high which suggests an efficacy of immunotherapy (13).

Indeed, in patients with recurrent and/or metastatic HNSCC, immune checkpoint inhibitors have shown efficacy and manageable safety. First, it has been shown that programmed cell death 1 (PD-1) inhibitors pembrolizumab and nivolumab improved overall survival compared with standard of care in patients with recurrent and/or metastatic HNSCC after a first line of platinum-based chemotherapy (8,14). Secondly, in patients with untreated recurrent and/or metastatic HNSCC, a polychemotherapy combining 5-fluorouracil (5-FU), platin, and

cetuximab (EXTREME regimen) has been compared to a monotherapy with pembrolizumab or a combination of 5-FU, platin, and pembrolizumab in the phase III KEYNOTE-048 trial (8). PD-L1 expression was characterized by the combined positive score (CPS), defined as the number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells × 100. In patients with a CPS ≥ 20 (40% to 45% of patients), pembrolizumab monotherapy improved OS compared to EXTREME with a median OS of 13.6 months versus 10.4 months (HR=0.65; 95%CI 0.53–0.80; p<0.0001). In patients with a CPS ≥ 1 (40% to 45% of patients), chemotherapy plus pembrolizumab improved OS versus EXTREME with a median OS of 14.9 months versus 10.7 months (HR=0.61; 95% CI 0.45–0.83; p=0.0007). These results changed the standard of care for these patients. Could immune checkpoint inhibitors improve the outcome of patients with locally disease when combined with radiation therapy?

Although ionizing radiations are known to induce tumor cell death via DNA damages, it has been shown that ionizing radiations may also eliminate tumors via the activation of immune response. For years, some teams have reported rare cases of patients with a cytotoxic effect of radiation therapy outside of the radiation field, known as the abscopal effect. The mechanism explaining this rare phenomenon has been elucidated recently: local radiation produces systemic immune-mediated effects (15). Indeed, ionizing radiations can induce immunological changes within the tumor microenvironment by facilitating tumor antigen release, increasing T cell infiltration, and up-regulate MHC-1 molecule on tumor cells (16). However, radiation can also attract immunosuppressive cells into the tumor microenvironment. Combining RT with immune checkpoint inhibitors could reverse this immunosuppressive effect in favor of immune system stimulation. Preclinical work demonstrated synergy between RT and immunotherapy. In a HNSCC mouse model, Oweida

et al demonstrated enhanced tumor control and improved survival when combining 10 Gy and a PD-L1 inhibitor (17). Tumor control was correlated with increased tumor T cell infiltration. In another mouse model of HPV-positive HNSCC, the combination of RT and PD-1 inhibitor activated of B cells (18).

Current questions are: could the combination of RT and checkpoint inhibitors increase local tumor control with additive or supra-additive effects? And can this combination induce abscopal effect?

3. Do checkpoints inhibitors increase tumor radiosensitivity?

In order to improve local control and survival of patients with HNSCC, combining radiation therapy with immune checkpoint inhibitors appears like a promising option. Many trials assessing this new association have been launched during the last five years but few results are currently available.

First, the combination of RT and immune checkpoint inhibitors has been assessed in patients ineligible to cisplatin. In a phase II study, 29 patients received RT with 3 cycles of concurrent pembrolizumab followed by 3 more cycles of pembrolizumab (19). Toxicities were typical of RT. However, 59% of grade 3-4 lymphopenia were reported. The 1-year OS and DFS rates were 86% and 76%, respectively.

In the randomized phase II GORTEC 2015-01 PEMBRORAD study, 133 patients were assigned to RT with cetuximab or to RT with pembrolizumab without maintenance treatment (20). Primary endpoint was the rate of locoregional control at 15 months. It was the same in the two arms (59% with cetuximab versus 60% with pembrolizumab, OR = 1.05, p=0.91). With a median follow-up of 25 months, the 2-year OS and DFS rates were also similar (OS: 55% versus 62%, respectively; PFS: 40% versus 42%). The compliance was very good with 92% of

patients receiving the planned dose of RT. Immunotherapy seems to have a better global tolerance with 88% of patients receiving the planned dose of immunotherapy versus 75% of patients who received the planned dose of cetuximab. The rates of grade3-4 mucositis and dermatitis were significantly lower in the pembrolizumab arm but with a higher rate of thyroid toxicity of any grade.

Concerning the combination of immune checkpoint inhibitors with RT and cisplatin, the first results were presented at ASCO in 2017 by Powell et al (21). In a small phase IB study, 27 patients were treated with standard CRT (70 Gy with weekly cisplatin) with concurrent pembrolizumab pursued after CRT for three months. The primary endpoint was the safety. These first results were reassuring with a good compliance and a safety profile similar to that of a CRT alone. This was confirmed in the publication of this study with a larger number of patients (22). Among the 59 included patients, 98% completed the full planned RT dose and 88% of patients received at least 200 mg/m^2 of cisplatin. Toxicities were similar to the ones usually reported, such as grade 3 dysphagia (44%) and mucositis (30%). At the end of the treatment, 85% of HPV+ patients and 78% of HPV- had a complete response. For HPV+ patients, 2-year OS was 97%. For HPV-, 1-year OS was 86.5%. Adding pembrolizumab to CRT seems safe with promising results.

In NRG-HN003 phase I study, patients with high-risk (ECS+ and/or R1) HPV- resected HNSCC received adjuvant CRT (60 to 66 Gy with weekly cisplatin) with pembrolizumab (200 mg every 3 weeks) for 8 doses in total, starting the week before CRT (23). Dose-limiting toxicity (DLT) was defined as grade 3 or higher non-hematologic toxicity related to pembrolizumab, immune-related toxicity requiring over two weeks of systemic steroids, or unacceptable RT delay. Among the first 12 included patients, only one DLT was reported (grade 3 fever requiring hospitalization). Twenty more patients were included in an expansion cohort with

3 more DLT (diverticulitis, wound infection, nausea). Overall, 94% of patients received the planned dose of cisplatin and pembrolizumab and 85% the planned dose of RT. The 1-year OS and DFS rates were 81% and 62%, respectively.

In another phase I study, RTOG 3504, nivolumab was combined with four different RT regimens (10 patients/arm) with a 3-month maintenance: CRT with weekly cisplatin, CRT with high dose cisplatin, RT with cetuximab, or RT alone (24). Administration of concurrent nivolumab was safe with only 3 DLT among the 39 included patients. However, compliance to maintenance nivolumab was very low after high-dose cisplatin or in patients unfit for cisplatin.

In REACH phase III trial (NCT02999087), patients with locally advanced HNSCC were randomized between an experimental arm combining RT with avelumab and cetuximab followed by 12 months of adjuvant avelumab, versus either CRT with cisplatin for patients fit for cisplatin or RT with cetuximab for unfit patients (20). Among the first 82 included patients, tolerance was good with 99% patients receiving the planned dose of RT and 88% receiving concurrent avelumab as planned. The rate of skin toxicity was not increased in the experimental arm compared to the RT+ cetuximab arm. Results on efficacy are pending

However, one phase III trial failed to show an improvement in survival. In this study, 697 patients were randomly assigned to CRT (70 Gy with high dose cisplatin) with placebo or with avelumab, an anti-PDL1 antibody (25). Avelumab was administered at a dose of 10 mg/kg every two weeks starting two weeks before CRT and continued for up to one year. Primary endpoint was PFS. At interim analysis, HR for PFS and overall OS were 1.21 (95% CI: 0.93-1.57; p=0.92) and 1.31 (95% CI: 0.93-1.85; p=0.94), respectively. Median PFS was not reached. The response rate was similar in the two arms (74% versus 75%). Tolerance was about the same in the two groups. However, more grade 3-4 adverse events were reported

in the avelumab arm with 80% versus 74% (25). Interestingly, it seems that the subgroup of patients with a level of expression of PDL1 superior to 25% at baseline could benefit of the addition of avelumab.

In this context, the results of the KEYNOTE-412 phase III study are eagerly awaited (26). In this study, 780 HNSCC patients are randomized between CRT (70 Gy with high dose cisplatin) + placebo or CRT + pembrolizumab (200 mg every 3 weeks up to one year). Primary endpoint is event free survival (NCT03040999).

The combination of RT and immune checkpoint inhibitors has also been evaluated in the adjuvant setting. For example, in ongoing NIVOPOSTOP phase III trial, patients with resected tumors with high risk factors of relapse are randomized between adjuvant CRT with cisplatin versus the same treatment combined with nivolumab (NCT03576417).

All these published data are rather disappointing. While the tolerance seems good, combination of immune checkpoint inhibitors with RT or CRT does not seem to improve its efficacy. In patients ineligible to cisplatin, it could be an alternative to cetuximab with a better tolerance.

4. Abscopal effect: an urban legend?

In metastatic HNSCC, use of RT and immunotherapy has drawn interest in order to induce abscopal effect defined as a reduction in metastatic disease burden outside of the targeted treatment area. RT is known to have a dual effect on the immune system: immunosuppressive with lymphopenia or increase of regulatory immune cells in tumor microenvironment but also immunogenic effect with liberation of neoantigens in particular when a high dose of radiation is used. Radiation induced neoantigens can boost

immunogenic effect through the activation of antigen-presenting cells and then CD8+ T cell priming able to recognize both the primary tumor and the metastatic sites (27).

For metastatic non small cell lung carcinomas, the pooled analysis of PEMBRO-RT and MDACC trials has shown a significant increase in response rate for unirradiated lesions when pembrolizumab is associated to RT compared to pembrolizuamb alone (41.7% versus 19.7%, OR=2.96, p= 0.004). Median OS was also significantly longer (19.2 months versus 8.7 months, p= 0.0004).

For HNSCC, several cases have already been described. For example, abscopal effect was observed in a patient with metastatic sinonasal squamous cell carcinoma treated with nivolumab 480 mg every 4 weeks after stereotactic body radiation (SBRT) at a dose of 30 Gy in 5 fractions to a single metastasis (28). Another case described an abscopal effect with a complete response of all lesions in a patient with poorly differentiated carcinoma treated with pembrolizumab after SBRT at a dose of 24 Gy in 3 fractions (29).

However, a single-center phase II trial found that the addition of SBRT to nivolumab did not improve the objective response rate of non irradiated lesions compared to nivolumab alone (30). In this study, 62 patients with metastatic HNSCC were randomly assigned to nivolumab at 3 mg/kg every 2 weeks with or without SBRT at a dose of 9 Gy in 3 fractions to one lesion. Objective response rates in non irradiated lesions were 29% with SBRT and 34.5% without (p=0.86). Overall survival was 14.2 months versus 13.9 months (p= 0.75). Toxicity was not statistically different in the two groups.

Another phase I-II trial is currently ongoing. It includes patients with extracranial metastatic HNSCC that received durvalumab, an anti-PDL1 antibody, at a dose of 1500 mg every 4 weeks, and tremelimumab, an anti-CTLA4, at a dose of 75 mg every 4 weeks, for 4 cycles with SBRT to a maximum of 5 sites (31). The first results seem to suggest a good tolerance, in

particular SBRT did not seem to add toxicity compared to the combination of immunotherapies. The response rate seems encouraging with an estimated median PFS of 7.2 months.

In conclusions, abscopal effect has been described in a minority of patients treated with immunotherapy and SBRT for metastatic HNSCC but failed to show outcome improvement in one phase II trial. However, more studies should be done to define the best therapeutic sequence when combining RT and immunotherapy in order to obtain an abscopal effect.

5. Perspectives

Even if these first results are disappointing, many questions are still unanswered, mainly about the optimal therapeutic sequence and the selection of patients. Indeed, in these first trials, immune checkpoint inhibitors have been used as if their action mechanisms were the same than a classical chemotherapy. They have been administered concurrently with radiation therapy and chemotherapy, mainly with cisplatin, and most often with a maintenance treatment ranging from 3 months to 1 year. Is it the best way to combine them? CRT may contribute to a severe immunosuppression status. Let's remember that the benefit of this combination has been proven in non small cell lung cancer first, with the results of PACIFIC trial (32). In this study, patients received a sequential treatment with a CRT followed by durvalumab, an anti-PDL1 antibody, every 2 weeks for 12 months starting 1 to 42 days after the completion of CRT. For HNSCC, two trials explore the question of the sequence: one NCI phase II randomized trial comparing a CRT (70 Gy with cisplatin) followed by pembrolizumab from week 10 to 31 versus the same CRT with concurrent pembrolizumab from week 1 to 22. In IMvoke010 phase III trial, patients with HNSCC with high risk of relapse are randomized after CRT between a sequential treatment with atezolizumab, an anti-PD1

antibody, for one year versus placebo (NCT03452137). Primary endpoint is overall survival. Of note, adjuvant treatment should start between 2 and 3 months after the end of CRT, a longer free interval than in PACIFIC trial.

Combining CRT with concurrent immunotherapy does not seem to be synergistic. One explanation of this lack of efficacy could be the immunosuppressive effect of large cervical lymph node areas irradiation. Indeed, Dammeijer et al showed that tumor-draining lymph nodes (TDLNs) play an important role in anti-tumor immune response induced by PD-L1 inhibitor in mouse models (33). In REWRITE phase II trial, patients non eligible to cisplatin with only homolateral involved lymph nodes receive RT at a dose of 70 Gy with concurrent durvalumab followed by adjuvant durvalumab for 6 months (NCT03726775). The originality of this study is that patients do not have contralateral elective node irradiation in order to protect TDLNs. The primary endpoint is non-irradiated neck nodal control rate.

Another related question is the necessity and duration of maintenance treatment. The PACIFIC trial has shown the benefit of an adjuvant treatment for non small cell lung cancer but HNSCC is a different disease with a minor risk to develop distant metastasis. Maintenance (or adjuvant) treatment has been proposed for HNSCC based on the results of studies for recurrent/metastatic tumors but we do not have solid data showing its efficacy for locally advanced tumors. Its length varies from 3 to 12 months without a strong rational.

Another approach is to use immunotherapy as neoadjuvant treatment. Uppaluri et al reported 44% of patients with pathological tumor necrosis after one cycle of neoadjuvant pembrolizumab followed 2 to 3 weeks later by surgery (34). In the ongoing KEYNOTE-689 phase III trial, patients with a resectable tumor are randomized between upfront surgery versus two cycles of pembrolizumab followed by surgery and adjuvant pembrolizumab. In

the two arms, adjuvant RT or CRT depends on pathological findings. The primary endpoint is major pathological response to neoadjuvant pembrolizumab and event free survival. Neoadjuvant nivolumab before CRT in patients with high-risk HPV positive tumors is also assessed in IMMUNEBOOST trial (NCT03838263). Primary endpoint is the feasibility of this combination.

For patients with recurrent/metastatic HNSCC, only those with a CPS > 1 benefit from immune checkpoint inhibitors. It could be the same for the combination with radiation therapy as suggested by the subgroup analysis of JAVELIN HN 100 trial (25). How to select the potential responders? In the CheckRad-CD8 multicenter phase II trial, patients with locally advanced HNSCC received a cycle of docetaxel-cisplatin combined with durvalumab and tremelimumab, an anti-CTL4. They had a tumor biopsy three weeks later. Patients with a pathological complete response (pCR) or with an increase in CD8 tissue infiltration of at least 20% compared to the initial biopsy received radiation therapy at a dose of 70 Gy with concurrent durvalumab and tremelimumab followed a maintenance treatment with durvalumab in maintenance for 8 months. The main objective was the feasibility with an expected rate of patients receiving radiotherapy + immunotherapy of at least 80%. Among the 80 patients included, 41 had pCR and 31 an increase in CD8 infiltrate. 82% received the combination. The 2-year progression-free and overall survival rates were 73% and 86%, respectively. However, 75% of patients experienced grade 3 or 4 toxicity, mainly dysphagia (53%), leukopenia (48%), or hepatitis (10%). This approach is interesting. However, if the survival data are encouraging, the significant toxicity of this combination raises questions, especially on the benefit of tremelimumab. A validation on a larger number of patients and in a randomized trial is mandatory.

To conclude, many questions are raised about the optimal dose, fractionation, timing, target volume, and field size of RT when combined with immunotherapy. Even if the first results are disappointing, there is still a lot of hope generated by these new therapeutic combinations.

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Table 1 - Selection of ongoing randomized trials assessing the combination of radiation therapy and immunotherapy for locally advanced head and neck squamous cell carcinoma.

NCT number	Phase	N pts	Treatment arm	Primary endpoint
NCT03452137 (IMVOKE010)	III	400	Adjuvant atezolizumab 1 year Placebo	EFS, OS
NCT03040999 (KEYNOTE-412)	III	780	CRT 70 Gy + cisplatin + pembro CRT 70 Gy + cisplatin + placebo	EFS
NCT03765918 (KEYNOTE-689)	III	704	Pembro x 2 - surgery - adjuvant pembro x 15 +/- (C)RT Surgery +/- (C)RT	mPR, EFS
NCT03576417 (NIVOPOSTOP)	III	680	CRT 70 Gy + cisplatin + nivo CRT 70 Gy + cisplatin	DFS
NCT03838263 (IMMUNEBOOST)	IIR	61	Nivolumab x 2 then CRT 70 Gy + cisplatin CRT 70 Gy + cisplatin	Feasibility

Abbreviations: N pts, number of patients; CRT, chemoradiotherapy; pembro, pembrolizumab; EFS, event free survival; OS, overall survival; DFS, disease free survival; mPR, major pathological response.