中文題目：高雄長庚醫院頭頸癌轉移的患者使用爾必得舒治療於免疫治療前與後的疾病無惡化存活期

英文題目：The progression free survival of Cetuximab before or after immunotherapy in head and neck cancer in Kaohsiung Chang Gung Medical Center experience

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***Background**:*
In the last decade, after cetuximab (anti-epidermal growth factor receptor), none of the novel investigated compounds has demonstrated benefit in head and neck squamous cell cancers (HNSCC), both in advanced and curative settings. Therefore, prognosis of recurrent/metastatic (R/M) HNSCC patients remains dismal, especially in platinum-refractory cohort. In the last few years, a new important class of drugs has affirmed its role. HNSCC, even if less 'immunogenic' than other malignancies (e.g. melanoma), was field of application of several new immune agents. To date, the most important data regard drugs acting on PD-1 (programmed death-1)/PD-L1 (programmed death-ligand 1) axis that is a crucial checkpoint used by tumor for immune escape (1). Cetuximab is the only drug with proven efficacy for the treatment of both locoregionally-advanced (LA) and recurrent/metastatic (R/M) disease. On-going trials evaluating cetuximab combinations with ICI and other immunotherapies might offer soon new treatment options in both LA and R/M HNSCC (2). Nivolumab appeared to improve efficacy versus IC regardless of prior cetuximab use, supporting its use in patients with R/M SCCHN with or without prior cetuximab exposure (3). In our health insurance, cetuximab and immunotherapy could not be used at the same time. If patient use one of the drugs, they could not apply the other under health insurance support at the same time. Most of the patients with head and neck cancer were in low economic status. They could not afford the immunotherapy in most situation. Therefore, we did a retrospective study to see if there were any benefit of immunotherapy before or after cetuximab injection.

Method:

Patients
We did a retrospective study at 1 single center in one country. Patients were eligible for enrolment if they met the following criteria: aged 18 years or older; had histologically or cytologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx, incurable by local therapies; had disease progression during or after platinum-containing treatment for recurrent or metastatic disease (or both) or recurrence or progression within 3-6 months of previous multimodal therapy containing platinum for locally advanced disease; received two or more lined od therapy for recurrent or metastatic disease; had at least one measurable lesion according to te Response Evaluation Criteria in Solid Tumors(RECIST), version 1.1; and had an Eastern cooperative oncology Group(ECOG) performance status score of 0, 1 or 2(on a five-point scale, with 0 indicating no symptoms and higher mumbers indicating greater disability).
Our patient received nivolumab or pembrolizumab at least once for recurrent or metastatic head and neck cancer under insurance cover or self-paid during period from 1 April 2017 to 20 March 2020 at 1 facility.

Patient were ineligible if they did not receive immunotherapy, or use only one time, loss follow up, not head and neck cancer.

Administration of nivolumab and pembrolizumab

Nivolumab and pembrolizumab were intravenously infused at a dose of 50mg to 200 mg at 2-3-6 week intervals. Image assessment was carried out after 3 months. Administration was continued until appearance of obvious progressive disease(PD) or unacceptable toxicity, or until the doctor in charge withdrew treatment for other reasons. However, even after confirmation of progression based on clinical or imaging findings, administration was continued when the doctor in charge considered that clinical benefit was likely.

Endpoints

The primary endpoint was progression free survival of the patient who receive immunotherapy and secondary endpoint was PFS between the patient who receive Erbitux before and after immunotherapy . Antitumour efficacy was determined by the doctor in charge at each facility based on RECIST version 1.1 guidelines. The doctors in charge and supervisors at each facility were all qualified head and neck cancer specialists. PFS and OS were also examined by the presence and absence of irAEs. To evaluate safety, Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 were used to examine adverse event occurrence rates by grade, deaths and the appearance of severe adverse events. TNM classification was performed in accordance with the 2009 version from the Unio Internationalis Contra Cancrum.

Result

Patients

Overall, 64 patients were included from 1 April 2017 to 20 March 2020. All of the patient were Taiwanese. Male and female 58 and 6(90.6%, 9.4%), Pembrolizumab usage showed 35 patients(54.7%), nivolumab showed 29 patients(45.3%). Fifty-five patients paid the IC by themselves, only nine patients were paid by the government. The average age showed 58.63 years old. There were only 10 people attend college. The ECOG showed 7 people in ECOG 0, 52 people in ECOG 1, 2 people in ECOG 4, 3 people in ECOG 3. In TNM, there was 3 patients were in stage III(4.7%), 19 patients in stage Iva(29.7%), 26 patients in stage IVb(40.6%), 16 patients in IVc(25%). 21 patients has PD-L1 below 50%, 19 people has had PDL-1 more than 50% and there was 24 people showed unknown percentage of PDL-1.

There were 15 people who receive immunotherapy before Erbitux, and 19 people received Erbitux before immunotherapy. Table 2 shows the baseline demographics of the patients enrolled in the study.

PFS

In our study, the estimate of the median PFS in months was similar between the immune before erbitux group (4.729 [95% CI 2.843–6.616]) and the immune after Erbitux group (4.535 [95% CI 2.821–6.249]). Immune before Erbitux compare to immune after Erbitux showed no difference in PFS. (Figure 1) Immune + Erbitux compare to immune only showed no difference in PFS as well (Figure A1-A5). The PFS in PDL-1 less than 50% showed 8.585 months (95% CI = 5.008–12.161) compare to PDL-1 more than 50% showed 6.374 months (95% CI = 4.438–8.311). The P value was 0.635.

Progression free survival
The Progression free survival in our study in patient who received immunotherapy was 6.297 months (Figure B1-B4)

Conclusion:
In our study, the progression free survival of the immunotherapy showed similar to the previous study. There was no difference between the patients who receive cetuximab before or after immunotherapy. In patient who has advanced head and neck cancer could consider cetuximab therapy first due to less economy cost compare to immunotherapy.

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