Nivolumab and sensorineural deafness

Introduction

Nivolumab (Opdivo®) is a human immunoglobuline G4 (IgG4) monoclonal antibody (HuMab) indicated either as monotherapy or in combination for the (adjuvant) treatment of *melanoma, non-small cell lung cancer, malignant pleural mesothelioma, renal-cell carcinoma, classical Hodgkin lymphoma, squamous-cell cancer of the head and neck, urothelial carcinoma, colorectal carcinoma, esophageal squamous cell carcinoma, and adenocarcinoma of the stomach, gastro-esophageal junction or esophagus* [1].
Nivolumab binds the programmed cell death receptor 1 (PD-1). PD-1 receptor is a negative regulator for T-cell activity which plays a role in the control of T cell immune responses when bound to its ligands. Ligands PD-L1 and PD-L2 are expressed in antigen-presenting cells under stimulation of tumor cells or other cells from the microenvironment of the tumor. Binding of PD-L1 and PD-L2 to the PD-1 receptor, negatively regulates T-cell activity [1]. Binding of Nivolumab to the PD-1 receptor, inhibits the binding of its ligands and allows (anti-tumor) T-cell responses. Nivolumab has been granted marketing authorization since the 19th of June 2015 in the European Union.

Other cancer therapies, such as cisplatin are known to trigger inflammation that results in hearing loss [2]. Immune related adverse events are common in treatment with immune checkpoint inhibitors, hearing loss, however, is not often described [3].

Reports

Until March 18th 2022, Lareb received one report on sensorineural deafness and Nivolumab.

Case NL-LRB-00743810: This spontaneous report from a physician concerns a female aged 40-50 years, with perceptive deafness following administration of nivolumab infusion for melanoma. Bilateral perceptive deafness (right 42 dB and left 53 dB hearing loss) started after the second course of Nivolumab (latency of 25 days) together with grade 3 hepatitis. Beside levonorgestrel, the patient did not receive comedication during nivolumab treatment. MRI cerebrum revealed no explanation for deafness; giving rise to a suspicion of an autoimmune inner ear disease. Deafness disappeared after prednisone treatment. The patient previously experienced a mild skin disorder which could also be immune-therapy induced. There were no signs of vertigo or tinnitus. The reporter confirmed that the deafness was not related to Vogt-Koyanagi-Harada, a syndrome which is described in the official product information and includes among others, hearing loss together with inflammatory symptoms of the eye.

Other sources of information

SmpC

Hearing loss or deafness is not mentioned in the Dutch SmpC of Nivolumab [1], nor in the product information of other immune checkpoint inhibitors except for ipilimumab (CTLA-4 inhibitor) [4]. However, Vogt-Koyanagi-Harada, which is a syndrome including hearing loss, together with skin- or eye disorders, is described in the SmpC [1].

Literature

Literature was searched specifically for hearing loss that was not part of the Vogt-Koyanagi-Harada syndrome to assess whether hearing loss could be an independent adverse reaction of nivolumab.

Up to 2019, two cases on pembrolizumab (another PDL-1/PD1 checkpoint inhibitor) and autoimmune sensorineural hearing loss were described [5, 6]. In 2019, another series of four cases on nivolumab (n=3) and nivolumab in combination with ipilimumab (n=1) associated with cochleovestibular disorders was published [7]. Since 2020, one case of unilateral autoimmune inner ear disease was described in a 69-year-old male patient with lung cancer, following the second dose of nivolumab. He gradually improved upon treatment with steroids [8]. A second patient, a 54-year-old male with metastatic melanoma, was described with recurrent bilateral hearing loss upon combined nivolumab and

ipilimumab treatment, 4 weeks after treatment completion [9]. Additionally, immune-related ototoxicity was described in association with six immune checkpoint inhibitors (PDL-1/PD1 and CTLA-4 inhibitors) in melanoma patients [10].

Other databases

Table 1. Reports on PDL-1/PD1 checkpoint inhibitors and sensorineural deafness from Eudravigilance [11] and WHO database [12].

Database	Drug	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Nivolumab	Deafness neurosensory[a]	1	-
Eudravigilance	Nivolumab[b]	Deafness neurosensory	17	2.08 (1.29 – 3.35)
	Nivolumab	Deafness bilateral	12	2.68 (1.52 – 4.74)
	Nivolumab	Deafness unilateral	4	0.29 (0.11 – 0.77)
	Pembrolizumab[c]	Deafness neurosensory	5	-
	Durvalumab	Deafness neurosensory	2	-
	Atezolizumab[d]	Deafness neurosensory	2	-
	Avelumab	Deafness neurosensory	-	-
	Cemiplimab	Deafness neurosensory	-	-
WHO	Nivolumab	Deafness neurosensory	19	3.22 (2.05 – 5.06)

[a]There were no other reports reported to Lareb on MedDRA HLT terms 'auditory nerve disorders' and 'hearing losses'.
[b]5 patients received nivolumab combination therapy (docetaxel: 1 case, ipilimumab: 3 cases, ipilimumab + carboplatin + paclitaxel: 1 case, trametinib + dabrafenib: 1 case).
[c]1 patient received pembrolizumab + ipilimumab
[d]1 patient received atezolizumab + bevacizumab
ROR was only calculated for nivolumab and deafness neurosensory associations with at least 3 cases.

The Eudravigilance database contained 32 reports on sensorineural deafness and PD-1/PDL-1 inhibitors. The following PD-1/PDL-1 inhibitors were included in the search: Nivolumab, Pembrolizumab, Durvalumab, Avelumab, Atezolizumab, Cemiplimab, Dostarlimab, Prolgolimab, Tislezlizumab and Retifanlimab.

15 reports were on nivolumab monotherapy, five reports on pembrolizumab monotherapy, two reports on durvalumab monotherapy and two reports on atezolizumab monotherapy. The other eight reports were on combination therapies, including nivolumab in combination with: ipilimumab (n=3), trametinib and dabrafenib (n=1), docetaxel (n=1) and ipilimumab, carboplatin and paclitaxel (n=1), and on pembrolizumab with ipilimumab (n=1) and one case on atezolizumab in combination with bevacizumab.

Four reports were confounded by previous or concomitant use of cisplatin, which is associated with the induction of deafness [2, 13]. Nine cases were previously treated with carboplatin, however, carboplatin is rarely associated with severe hearing loss when used without cisplatin [14], hence this was not considered a risk factor. In three cases, deafness was part of the Vogt-Koyanagi syndrome, which is described in the official product information of nivolumab. In another six reports, deafness was reported together with uveitis, which is also a symptom of the Vogt-Koyanagi syndrome. Moreover, there were five cases where brain neoplasms or metastasis could have played a role in hearing loss. Although in one of these cases the neurosurgery department was consulted and the brain metastasis was ruled out as a cause for the deafness.

14 reports remained, where no other risk factors for hearing loss or sensorineural deafness were reported.
Some of these are described in more detail in the supplementary files.

Prescription data

Table 2. Number of patients using Nivolumab (L01XC17) and other checkpoint inhibitors in the Netherlands [15].

Drug		2017	2018	2019	2020	2021
L01XC17	Nivolumab	2,551	2,784	3,522	3,338	2,780
L01XC18	Pembrolizumab	1,173	2,564	4,336	5,744	6,060
L01XC28	Durvalumab	.	.	466	969	1,137
L01XC32	Atezolizumab	.	82	217	191	229
L01XC31	Avelumab	5	33	52	49	47
L01XC33	Cemiplimab	.	.	.	.	54
L01XC11	Ipilimumab*	282	461	568	837	782

*Ipilimumab is a CTLA-4 inhibitor, the others are PD-1/PDL1 checkpoint inhibitors.

Mechanism

It is postulated that immune checkpoint inhibitors may affect the cochlear homeostasis and function of cochlea tissue. Especially a preservation of outer hair cell and an increase in macrophage activity appeared in the high frequency (>32 kHz) basal part of the cochlea in a mouse model [16].

Discussion and conclusion

The Netherlands Pharmacovigilance Center Lareb has received one case of sensorineural hearing loss in a patient using nivolumab. Hearing loss is not described in the Dutch SmPC of nivolumab or other PDL-1/PD-1 checkpoint inhibitors. Since the Vogt-Koyanagi-Harada syndrome, which includes hearing loss, is described in the Dutch SmPC of nivolumab, we assessed whether hearing loss could be an independent adverse drug reaction. The association between nivolumab and sensorineural hearing loss is disproportionate in the Eudravigilance and WHO databases. Multiple case reports have been described in literature on sensorineural hearing loss and PD-1/PDL-1 (e.g. nivolumab, pembrolizumab) or other checkpoint inhibitors (CTLA-4, ipilimumab). Check-point inhibitors can cause immune related adverse events and may affect the cochlear homeostasis and function of cochlea tissue. Therefore, sensorineural hearing loss as a result of check-point inhibitors is possible and attention to this adverse drug reaction is warranted.

References

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This signal has been raised on May 23, 2022. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl

Supplementary files

Case A: AU-BRISTOL-MYERS SQUIBB COMPANY-BMS-2020-106926. This literature post marketing case was reported in an article and describes the occurrence of unilateral autoimmune sensorineural deafness in a 69-year-old male patient. The patient was initially diagnosed with early stage non-small cell lung cancer of the right upper lobe of the lung in 2016. This lesion was resected and no adjuvant chemotherapy or radiotherapy was offered at that point. Two years later the patient developed recurrent disease at the resection site. He received carboplatin and paclitaxel concurrently with radiotherapy over 6 weeks. Due to disease progression, the patient was treated with nivolumab. After the second dose of nivolumab, the patient experienced unilateral right-sided hearing loss. Unilateral sensorineural deafness was diagnosed on audiometry at both high- and low-frequency levels. An MRI brain scan revealed no evidence of central nervous system involvement. As no clear cause was evident on initial assessment to explain the hearing loss, the suspicion of immune related ototoxicity was raised. He commenced high-dose intravenous methylprednisolone for 3 days, followed by a slow wean of oral prednisolone. The patient had a gradual improvement in hearing. Repeat audiology confirmed reversal of the sensorineural deafness over time. Tomography (PET)/CT imaging post-nivolumab demonstrated a marked reduction of fluorodeoxyglucose (FDG) avidity, consistent with a complete metabolic response to immunotherapy. Based on this and on the neurotoxicity, the patient remained off systemic treatment. He remains in follow-up and is clinically well. Sequential scans demonstrate ongoing stability with metabolically inactive disease. Repeated audiology showed further evidence of improvement in the hearing of the right ear.

Literature case report: Rajapakse A, O'leary C, Gundelach R, Deva R, O'Byrne O. Unilateral autoimmune inner ear disease in a patient with lung cancer treated with nivolumab. Oxford Medical Case Reports. 2020;9:326-9

Case B: AU-009507513-1503AUS003947. This report from an investigator of a phase I/II clinical trial study is regarding a 57-year-old male subject treated with ipilimumab and pembrolizumab for malignant melanoma. After 23 days, the subject experienced (bilateral) sensorineural hearing loss, which was initially presumed to be middle ear infection. For that reason, antibiotic treatment with erythromycin was commenced. The left middle ear infection was also treated with sulfamethoxazole / trimethoprim. Despite the treatment, hearing loss persisted. Subsequently, it was found to be potentially autoimmune related, during an ear, nose, throat surgeon review. The patient was treated with methylprednisolone (intravenously) and the reaction recovered/resolved.

Case C: DE-BRISTOL-MYERS SQUIBB COMPANY-BMS-2018-114863. A physician reported that a 79-years-old female patient experienced sensorineural deafness (more pronounced on the right side than the left) soon after her second cycle (latency: 1 month) of nivolumab for early reccuring Hodgkin lymphoma. The patient continued nivolumab treatment as, due to being second line treatment, it was her last chance. Previously, the patient had received 4 cycles of adriamycin + vinblastine + dacarbazine and 8 cycles of brentuximab. The deafness showed marked progression after the third administration of nivolumab. The fourth nivolumab cycle was not administered and a cortisone bolus therapy attempt was performed. The patient was treated with oral prednisolone. There were no changes in laboratory values associated with the event. Alternative etiologies had mostly been ruled out. The reaction was not recovered at the time of reporting.