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REVIEW ARTICLE

Ototoxicity in Immune Checkpoint Inhibitors Therapy

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

Introduction: Immune checkpoint inhibitors (ICIs) and T-cell therapies are a modern, well-established cancer treatment. The priority of oncological treatment is to cure cancer. However, treatment-related toxicities, i.e. immune-related adverse events (irAEs), continue to emerge and are not that well understood yet. ICIs can cause profound, multiple, and diverse irAEs – the sequelae of unknown mechanisms. One of the organs susceptible to collateral damage is the hearing organ. Complications related to hearing, tinnitus, and balance disorders are extremely burdensome and significantly impair many aspects of the quality of life of patients and survivors.

Aim: The aim of the work is to review the literature in the area of ototoxicity of ICIs.

Materials and method: A systematic search of the Web of Science, PubMed, and Embase databases for studies published until 1 March 2022 was conducted.

Results: Reported clinical symptoms ranged from sudden bilateral hearing loss and imbalance to mild hearing loss or tinnitus with preserved hearing. It was found that the median time from ICI initiation to hearing loss development was 3 months. The hearing impairment was secondary to bilateral sensorineural hearing loss in the majority of patients (>60%), and at least one other irAE accompanied the hearing loss in 2/3 of patients. Hearing loss significantly improved in 45.7% of the patients.

Conclusions: The majority of cases of ICI-related hearing loss presented in the literature were reversible. Therefore, it is important to develop and implement routine therapeutic algorithms. Further research is needed to define the true prevalence of ICI-related hearing loss, optimal diagnostics, and management.

KEYWORDS: hearing loss, ICI, immune-related adverse events, ototoxicity

ABBREVIATIONS

AHF – audiometry of high frequencies
DPOAE – distortion product otoacustic emission
FDA – Food and Drug Administration
ICIs – immune checkpoint inhibitors
IL-2 – interleukin-2
irAEs – immune-related adverse events
NCCN – National Comprehensive Cancer Network
OAE – otoacoustic emissions
PD – programmed death
PD-1 – programmed death-1
PDL-1 – programmed death ligand-1
TIL – tumor-infiltrating lymphocyte

INTRODUCTION

Immune checkpoint inhibitors (ICIs) and T-cell therapies are a modern, well-established cancer treatment. Since the United States Food and Drug Administration (FDA) approved ipilimumab in 2011, six additional ICIs have received approvals, including programmed death-1 (PD-1) inhibitors - nivolumab, pembrolizumab, and cemiplimab, as well as programmed death ligand-1 (PDL-1) inhibitors – atezolizumab, avelumab, and durvalumab. Targeting additional checkpoints with new compounds and using various combinations of ICIs and T-cell therapies with or without traditional treatment modalities provide huge potential for the future [1]. The priority of oncological treatment is to cure cancer – however, treatment-related toxicities, i.e. immune-related adverse events (irAEs), continue to emerge and are not as well understood yet as the side effects caused by traditional chemotherapy agents. ICIs can cause profound, multiple, and diverse irAEs in still unknown mechanisms. The host's genetic background is likely to play a role in irAE susceptibility for the presentation of toxicity varies among patients [2]. Adverse events are also thought to be reflective of a bystander process that indicates a treatment – responsive host immune system; renal cancer patients who experienced irAEs had significantly better clinical outcomes when treated with ICI-

Tab. I. Literature review: patients' series with hearing loss after receiving ICI for cancer therapy.

PUBLICATION	TUMOR TYPE, *ICI THERAPY	**irAEs
Page et al. [1]	3 metastatic melanomas: TIL therapy, pembrolizumab, dabrafenib, trametinib, ipilimumab, nivolumab, fludarabine, cyclophosphamide, aldesleukin1 metastatic renal cell carcinoma: ipilimumab, nivolumab.	67% of patients treated with steroids had substantial improvements in hearing.
Rosner et al. [8]	3 metastatic melanomas: interleukin-2 (IL-2) followed by carboplatin plus paclitaxel combination chemotherapy. He then received nivolumab.	ICI-mediated ototoxicity early in their treatment course, manifested most commonly as bilateral tinnitus with or without high-frequency hearing loss and speech and/or word recognition deficits; 1 patient – tinnitus without subjective hearing loss, 4 patients with sensoneural hearing loss, oral corticosteroids were administered, 1 patient – symptoms stabilized without intervention.
Stürmer et al. [9]	3 - stage IV melanoma patients.	sudden onset of otovestibular dysfunction (hearing loss and vestibulopathy).

*ICI – Immune checkpoint inhibitors; ** irAEs – immune-related adverse events.

-based regimens. What is more, the analysis showed that patients who experienced any irAEs early in ICI treatment initiation had significantly longer overall survival [3].

One of the organs susceptible to collateral damage is the hearing organ. It can be impaired at many levels and via many mechanisms during chemotherapy, which is a well-known phenomenon. Nevertheless, there is much less experience in ICI ototoxicity.

Hearing problems are very common – approximately 300 million people worldwide suffer from them. The incidence of hearing loss varies depending on age. Among people over 75 years of age, approximately 35% of respondents have hearing loss, and in the group of people between 65 and 74 years of age – 23%. The hearing loss rate curve increases exponentially for each age category. It may develop as a result of changes occurring in the receiving section of the hearing organ or in the sound conduction apparatus, or it may be of a mixed nature. Of importance is the fact that an ear with previous hearing loss is much more susceptible to further damage than an ear with normal hearing.

The first case of ototoxicity caused by ICI therapy was delivered in 2016 [4], followed by two cases in 2019 [5, 6]; then, the recurrent audiovestibular toxicity was described in 2020 [7]. Rosner et al. [8] published the largest series to date, with six patients. The remaining cases are smaller sets [1, 9] or individual case reports [10–15]. At the time of manuscript preparation, there were 38 cases of ICI-related audiovestibular irAEs in the literature [16].

The number of patients treated with ICI will increase exponentially due to greater morbidity on the one hand, and greater availability of therapy on the other hand. Therefore, more irAEs should be expected. Complications related to hearing, tinnitus, and balance disorders do not appear to have significant consequences on the patient's overall health, but they are extremely burdensome and significantly impair many aspects of the quality of life of patients and survivors.

We hypothesize that the overlapping health problems of the population: hearing loss, tinnitus, dizziness, with the increasing use of ICIs in times of mass incidence of cancer, will result in a higher rate of hearing complications.

AIM

The aim of the work is to present own experiences and review the literature in the subject area.

MATERIALS AND METHOD

A systematic search of the Web of Science, PubMed, and Embase databases for studies published until 1 March 2022 was conducted. The selected MeSH search terms were "hearing loss" OR "hearing impairment" OR "ototoxicity" OR "vestibular toxicity" OR "audiovestibular toxicity" AND "immune checkpoint inhibitor" OR "immunotherapy". Literature review was consistent with the criteria.

RESULTS

Tab. I. presents a summary of available literature data on the ototoxicity of ICI therapy. To date, there has been a small number of reports of patients with isolated hearing loss after receiving ICI for cancer therapy [4, 5, 6, 17]. Reported clinical symptoms ranged from sudden bilateral hearing loss and imbalance to mild hearing loss or tinnitus with preserved hearing. It was found that the median time from ICI initiation to hearing loss development was 3 months. Melanoma was the most frequent diagnosis (73.7%) [16]. Hearing impairment was secondary to bilateral sensorineural hearing loss in the majority of patients (>60%), and at least one other irAE accompanied the hearing loss in 2/3 of patients. Hearing loss significantly improved in 45.7% of the patients. In the meta-analysis that covered the biggest number of patients so far, the overall response rate and disease control rate were 67.6% and 85.3%, respectively [16].

DISCUSSION

Monitoring for ototoxic drug effects is the standard of care. Diagnostic and prevention programs for hearing loss induced by ototoxic drugs should be implemented in every patient for whom such a therapy is planned; potential ototoxicity should be discussed with the patient and included in the treatment plan. Unfortunately, few oncological departments providing chemotherapy or ICI have access to otological facilities, equipment, and human resources.

What is more, no recommendations exist within NCCN guidelines or other similar multidisciplinary panel guidelines with regard to the identification and management of audiovestibular irAEs [18, 19].

Problems that need to be solved before implementing ICIs and T-cell therapies are as follows:

1. Guidelines for monitoring drug ototoxicity using audiological methods are not well developed and are not routinely performed in adult oncology patients.

2. Efforts should be directed at creating parallel programs: detecting hearing loss on an ongoing basis in patients currently undergoing treatment, assessing the impact of loss symptoms on the quality of life of patients.

3. The program for monitoring the ototoxic effects of ICIs should be conducted by a specialist in this field. Doctor's visit and baseline tests should be performed before the first dose of treatment is administered.

4. Selection of audiological tests should be appropriate:

   - Pure-tone audiometry of high frequencies 9–16 or 20 kHz (AHF) is the most sensitive test, which allows for diagnosis of the preclinical loss of cochlear function.
   - Otoacoustic emissions (OAE), or more precisely, otoacoustic distortion products (DPOAE) are another tool for the sensitivity of hearing loss measurement; this is an objective test but not dedicated to hearing neuropathy testing.
   - Some centers suggest using only pure tone audiometry, believing that high-frequency audiometry may be too sensitive and too aggressive in influencing the treatment plan [20]. Existing high-frequency hearing loss has a negative impact on the usefulness of high-frequency audiometry and otoacoustic emissions. Cytotoxic agent--induced hearing loss most often first appears an octave below the highest audible frequency. There is a consensus on the use of DPOAEs, which is justified by the fact that changes in their level precede the decline of the auditory curve recorded in pure tone audiometry.

The falling threshold curves in adjacent frequencies indicate the probability of actual damage to the hearing organ. Therefore, any decline in the threshold curve should be an indication to repeat the test within 24 hours and report it to the doctor supervising the therapy. However, this does not necessarily have an absolute impact on the treatment plan. Administration of corticosteroids may provide symptom improvement. Otherwise, hearing aid placement may be recommended. The decision of whether to hold or permanently discontinue ICI is difficult and requires further multidisciplinary discussion before providing exact guidance. Such a decision would involve weighing the severity of ototoxicity, clinical benefit of ICIs, and the potential reversibility of their toxicity [8].

Diagnosing the presence of hearing loss before treatment allows to identify risk factors, talk to the patient and determine the baseline level of hearing loss for further monitoring and rehabilitation. The patient must be informed about the significant risk of deterioration of hearing quality and the possibility of tinnitus, which for many patients is a much greater discomfort than the hearing loss itself, whereas the patient is rarely aware of the direct connection between the two symptoms. The use of toxic agents such as aminoglycoside antibiotics or loop diuretics (furosemide) should be definitely avoided (within the limits of therapeutic possibilities), as they may significantly intensify the ototoxicity of chemotherapy. Avoiding noise, which may increase ototoxic effects, is a basic recommendation that can be implemented in the vast majority of cases.

CONCLUSIONS

With the expanded use of ICIs in the different treatment regimens and adjuvant settings, the number of survivors with ICI-related hearing loss is expected to increase; moreover, this sequela of treatment is associated with a high response rate to ICIs. Most of the cases of ICI-related hearing loss presented in the literature were reversible. Therefore, it is important to develop and implement routine therapeutic algorithms. Further research is needed to define the true prevalence of ICI-related hearing loss, optimal diagnostics, and management.

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Table of content: https://otolaryngologypl.com/issue/16240 Tables: 1 Figures: – References: 20

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