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Audiovestibular Dysfunction Associated with Adoptive Cell Immunotherapy for Melanoma

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Abstract

Objective.—To understand the audiologic and vestibular toxicities associated with adoptive cell immunotherapy (ACI) targeting pigment-pathway antigens on melanoma and to investigate the use of intratympanic steroid injections in the treatment of these toxicities.

Study Design.—Prospective nonrandomized study.

Setting.—Tertiary clinical research center.

Methods.—Thirty-two patients with progressive metastatic melanoma who failed conventional therapy underwent ACI with T cells genetically modified to target MART-1 (n = 18) or gp100 (n = 14). All patients received serial audiometric testing. Vestibular testing was performed on patients

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with vestibular complaints. Patients with significant deficits received intratympanic steroid injections.

Results.—Of 32 patients, 15 had no hearing change, 9 had mild hearing loss, and 8 had moderate hearing loss following treatment. Ten patients received intratympanic steroid injections for mild ($n = 2$) or moderate ($n = 7$) hearing loss or for significant imbalance ($n = 1$). Of those with mild hearing loss ($n = 9$), all but 1 recovered to pretreatment hearing levels. Four of 8 patients with moderate hearing loss recovered to baseline hearing levels, and 4 had partial recovery. All 7 patients with posttreatment vestibular complaints had demonstrable vestibular dysfunction. Three of these patients demonstrated recovery to normal vestibular function. The number of modified T cells infused for therapy correlated with the degree of audiovestibular deficit.

Conclusion.—Adoptive cell immunotherapy targeting pigment-pathway cell proteins, a novel therapy for melanoma, can induce hearing loss and vestibular dysfunction. The presumed mechanism of autoimmune attack on normal melanocytes in the cochlear stria vascularis and in the vestibular organs demonstrates the importance of melanocytes in normal inner ear function.

Keywords

melanoma; melanocytes; stria vascularis; cochlea; vestibular organs; audiovestibular dysfunction; hearing loss; vestibular dysfunction; adoptive cell immunotherapy

Tumor-associated antigens (TAAs) have been recognized in a variety of human cancers and are a target for novel cancer therapies that are under development.¹ These antigens can be mutated proteins specific to a certain tumor; however, many of them are normal, non-mutated self-proteins that are selectively expressed or overexpressed in certain tumors. Adoptive cell immunotherapy (ACI) uses T cells specific for these antigens, which are activated and expanded in vitro and administered to the patient after lymphodepletion. This can then confer tumor reactivity, overcome tolerance, and lead to tumor regression.^{1,2} Adoptive cell immunotherapy using T cell receptors (TCRs) capable of recognizing 2 specific TAAs, gp100 and MART-1 (melanoma antigen recognized by T cells 1), holds promise for the treatment of melanoma.¹

Many TAAs are expressed in normal cells throughout the body, leading to various related toxicities when using ACI. The TAAs associated with melanoma, for example, are also expressed in normal melanocytes in the skin, eye, and ear.^{1,3} Adoptive cell immunotherapy targeting melanoma has been shown to result in ocular inflammation and vitiligo presumably as a result of autoimmune destruction of normal melanocytes in the eye and skin.^{1,4,5} Melanocytes are also found in the intermediate layer of the stria vascularis of the cochlea, as well as in the dark cells of the vestibular organs.^{6,7} Therefore, autoimmune destruction of melanocytes in the inner ear may lead to audiovestibular dysfunction.

We present audiovestibular findings in patients with metastatic melanoma treated with ACI targeting pigment pathway proteins associated with melanoma, gp100 and MART-1. Some patients demonstrated audiovestibular dysfunction, presumably due to autoimmune destruction of melanocytes in the inner ear. These findings are important not only to the design of immunotherapies targeting TAAs, but also to the overall understanding of autoimmune hearing loss. We discuss the frequency, severity, temporal relationship, and

factors facilitating recovery of audiovestibular dysfunction in a series of patients receiving ACI treatments targeting gp100 and MART-1 for metastatic melanoma.

Methods

Thirty-two patients, aged 31 to 63 years (mean, 47.7 years), with progressive metastatic melanoma were enrolled in protocols at the National Institutes of Health (Bethesda, Maryland) between July 2007 and September 2008 to undergo ACI with TCRs targeting either gp100 or MART-1.^{1,2} The protocols were approved by the National Cancer Institute's Institutional Review Board. All had failed conventional therapy, which included at least high-dose inter-leukin-2 (IL-2). After receiving a lymphodepleting, nonmyeloablative regimen of cyclophosphamide and fludarabine, patients received an infusion of their own peripheral blood lymphocytes retrovirally transduced to express an anti-gp100 TCR (n = 14) or an anti-MART-1 TCR (n = 18). Following T cell infusion, both groups were given a high-dose bolus of IL-2 to tolerance. Leukocyte and platelet counts were allowed to recover spontaneously.

Subsequent to documentation of a treatment-associated hearing loss after T cell infusion in an initial patient, prospective serial audiometric testing was initiated for all protocol patients. This consisted of a baseline assessment prior to ACI and follow-up testing after completion of ACI, typically within 10 days of infusion. Audiometric evaluation included pure-tone thresholds from 250 to 8000 Hz. The degree of hearing loss, based on the 500/1000/2000/4000-Hz pure-tone threshold average, was classified as mild (>20 and 40 dB hearing level [HL]), moderate (>40 and 70 dB HL), severe (>70 and 95 dB HL), and profound (>95 dB HL). A significant change in hearing was defined as a worsening in audiometric thresholds by 10 dB for 2 consecutive frequencies or 20 dB for a single frequency.⁸ One patient had no pre-ACI audiogram and was excluded from data analysis. Two additional patients had metastatic leptomeningeal melanoma involving the audiovestibular cranial nerves and were not included in the data analysis.

Patients with post-ACI audiovestibular changes received additional serial follow-up audiometry, vestibular testing, and neurologic evaluation and treatment as indicated by their symptoms. Patients with subjective change in hearing in addition to significant threshold shifts, resulting in a hearing loss of a mild or greater degree, were offered a series of 1 to 3 intratympanic steroid injections of dexamethasone (24 mg/mL) or methylprednisolone (62.5 mg/mL) according to the method described by Haynes et al.⁹ Systemic steroid therapy was not used to avoid any systemic interference with the antitumor effects of ACI. Patients with post-ACI vestibular symptoms underwent comprehensive vestibular evaluation that included, as tolerated, videonystagmography (VNG), rotational vestibular testing (RVT), and posturography. Pretreatment vestibular testing was not performed. Patients with significant deficits in vestibular function were also offered intratympanic steroid injections.

Statistical Analysis

Descriptive statistical analysis was performed, and data comparisons were analyzed with the Student *t* test, Fisher exact test, and χ^2 test, as appropriate.

Results

Of the 32 patients, 15 (46.9%) had no change in hearing following treatment with ACI. Seventeen (53.1%) demonstrated deterioration in hearing, resulting in mild hearing loss in 9 patients (28.1%) and moderate hearing loss in 8(25.0%). For the patients with post-ACI change in hearing, the average decline in the 4-frequency pure-tone average was 22.7 dB (range, 10.0–52.5 dB). Mean (SD) follow-up after the baseline audiogram was 4.2 (7.0) months (range, 1–37 months). When comparing hearing outcomes between the MART-1 and gp-100 treatment groups, there was no significant difference in the occurrence of hearing loss or the degree of change in hearing ($P = .73$ and $P = .15$, respectively). Therefore, the data were analyzed as one cohort.

Patients with deterioration in hearing reported audiovestibular symptoms starting an average of 9.5 days (range, 0–36 days) after the initial cell ACI infusion. The most common symptom was aural fullness, reported by 10 patients. Other symptoms included subjective change in hearing reported by 9 patients, dizziness or imbalance reported by 3 patients, and tinnitus reported by 2 patients.

Evaluating the pretreatment otologic history of patients with prior potential cochlear insults or preexisting high-frequency hearing loss revealed no significant differences in the hearing deterioration group vs those with stable hearing ($P = .48$ and $P = .44$, respectively) (Figure 1). Age was not significantly different between those with post-ACI hearing decline and those with stable hearing ($P = .95$).

Patients with a subjective change in hearing and a significant decrease in hearing thresholds after their ACI infusion were offered a series of 1 to 3 intratympanic steroid injections, depending on patient availability. Methylprednisolone was initially used for 3 patients but was discontinued because of associated otalgia. Subsequently, dexamethasone was used for 7 patients. A total of 10 patients received injections: 7 with a post-ACI change in hearing to a moderate level, 2 with a post-ACI change to a mild level, and 1 with significant vestibular symptoms and no post-ACI hearing loss. The 2 patients with mild hearing loss recovered to baseline hearing levels after the injections. Of those patients with a moderate hearing loss, 3 patients recovered hearing to pretreatment levels, whereas 4 had partial recovery. The patient receiving steroid injections for vestibular dysfunction recovered to normal objective vestibular function on testing.

Overall, 12 of 17 (70.6%) patients with a post-ACI change in hearing recovered to their baseline hearing level, including 5 patients who received intratympanic steroid injections. Of those with an onset of mild hearing loss, 8 of 9 (88.9%) recovered to baseline hearing levels and 1 (11.1%) had partial recovery of hearing. Of those with deterioration to a moderate hearing loss, 4 of 8 recovered to baseline and 4 had partial recovery of hearing. A permanent change in hearing from baseline pretreatment levels was documented in 5 of 32 (15.6%) patients.

Seven patients with post-ACI vestibular complaints underwent vestibular testing as tolerated, including VNG, RVT, and posturography. Complaints ranged from minor dizziness or lightheadedness to severe oscillopsia and imbalance requiring an assistive walking device for

2 patients. One additional patient with vestibular complaints was found to have benign paroxysmal positional vertigo and was not included in our analysis. All 7 patients tested had either bilateral hypofunction or no response on caloric testing. Six patients underwent RVT; 4 showed reduced vestibuloocular reflex (VOR) gain suggestive of bilateral vestibulopathy, and 2 demonstrated normal VOR gain. Six patients underwent posturography testing. Five of these patients had decreased sensory organization composite scores and reduced performance on vestibular-dependent test conditions, conditions 5 and 6. Overall, 3 patients with vestibular findings had recovery of the VOR to within normal limits, 1 had partial recovery, and 3 had no improvement on vestibular testing. Of the 4 patients with persistent objective evidence of bilateral vestibular dysfunction, 3 had subjective improvement in their vestibular symptoms with no significant functional limitations over time, despite persistent oscillopsia.

A dose-response relationship was seen between audiovestibular dysfunction and ACI. Patients with stable hearing received a significantly lower ACI dose than those with mild or moderate hearing loss ($P < .0001$). All patients with any degree of hearing loss after ACI were transfused with more than 10×10^9 T cells (Figures 2 and 3, Table 1). There was a similar association in patients with vestibular dysfunction. Patients without vestibular dysfunction received a substantially lower dose of infused T cells for therapy than patients with vestibular dysfunction ($P = .007$) (Figure 4, Table 1).

Other immune-mediated toxicities, such as posttreatment rash and uveitis, were observed in the majority of patients. Three patients did not have rash or uveitis, and none of these patients had posttreatment hearing loss. The development of a rash was pervasive and did not statistically associate with post-treatment change in hearing ($P = .38$). However, the presence of uveitis and posttreatment hearing loss was correlated ($P = .03$). Neither uveitis nor rash correlated with higher doses of T cells for ACI ($P = .38$ and $P = .40$, respectively). In follow-up, many patients were noted to develop vitiligo and poliosis, but these data were not included, as they were unavailable at the time of data analysis.

Discussion

Gene therapy regimens have been developed to target different cancers, including colorectal carcinoma, breast cancer, and melanoma.¹ These ACI therapies target TAAs by infusing autogenous lymphocytes transduced with high-avidity TCR with antitumor reactivity into a lymphodepleted host. The largest experience comes from targeting proteins of the pigment production pathway in patients with melanoma.¹

Our data demonstrate a dose-response relationship between audiovestibular dysfunction and ACI transferred cell dose, which provides indirect evidence that modified T cells with activity against MART-1 and gp100 were responsible for an autoimmune attack on the structures of the inner ear. Patients receiving a low-dose transfusion of T cells for treatment had no hearing loss or vestibular symptoms. The lower T cell dose associated with hearing loss than vestibular symptoms may suggest that melanocyte dysfunction has a more detrimental effect on homeostasis of the endolymphatic potential in the cochlea than it does in the vestibular end organs or that there may be differential T cell penetration into these end

organs. This, however, may also represent a selection bias, as not all patients underwent objective vestibular testing.

It is known that melanocytes are found in the intermediate layer of the stria vascularis in the cochlea. The stria vascularis of the cochlea contains N^+K^+ -ATPase and potassium channels that are essential for maintaining the endocochlear potential.^{6,7} Disruption of the endocochlear potential has been shown to result in hearing loss.⁶ The hearing loss in our patients is most likely a result of destruction of melanocytes in the stria vascularis, leading to a disruption of the rapid recycling of potassium ions from the organ of Corti to the endolymph and a subsequent decrease in the endocochlear potential.¹⁰ A similar mechanism presumably leads to vestibular dysfunction.

The proposed mechanism has immunologic implications as well. Other autoimmune diseases or immunologic therapies that target antigens or cells found in the inner ear could cause similar outcomes. This mechanism is similar to that seen in Vogt-Koyanagi-Harada (VKH) disease, in which there is auto-immune destruction of melanocytes in the eye, inner ear, skin, and hair.¹ Analysis of the ocular aqueous humor of VKH patients demonstrates T cells with antityrosinase and anti-gp100 reactivity.¹¹ This supports our observation that patients receiving ACI develop inflammatory responses and toxicities in the organs where melanocytes are normally present.

Although ACI led to audiovestibular dysfunction, the vast majority of patients with hearing deterioration recovered to their audiometric baseline (12 of 17; 70.6%). Although 5 patients were left with a permanent change in hearing, all of these patients exhibited some degree of hearing improvement. The recovery of hearing could suggest melanocyte recovery in the stria vascularis after depletion of the TAA-targeting T cells from the inner ear. Fifty-six percent of patients receiving intratympanic steroid injections recovered their hearing to pre-ACI levels. However, the efficacy of intratympanic steroid injections to salvage audiovestibular recovery is uncertain, as our small cohort was biased and included only those patients with the greatest degree of posttreatment hearing decline. In addition, the timing of intratympanic steroid administration varied due to prolonged post-ACI recovery periods in some patients, precluding early identification of hearing loss. We also acknowledge that the patients who recovered audiovestibular function after steroid injection may have recovered without intervention.

The rate of vestibular recovery from bilateral vestibulopathy was lower than that of hearing recovery, with only 3 of 7 patients regaining normal objective vestibular function. Despite the lack of full recovery on vestibular testing, 3 patients subjectively improved. These findings underscore the adaptation of the central nervous system to peripheral vestibular insult, as can be seen in other vestibular disorders, such as viral labyrinthitis.¹²

Others have suggested that prior insult to the inner ear such as acoustic trauma may increase susceptibility to ototoxic agents (eg, cisplatin and aminoglycosides).¹³ However, we did not find a significant relationship between post-ACI decline in hearing and pretreatment potential cochlear insults or preexisting hearing loss. This could be due to the fact that ACI

targeted specifically melanocytes, which are likely not the primary target of previous ototoxic agents and audiovestibular insults.

Hearing loss and vestibular dysfunction were found in many patients undergoing ACI targeting gp100 and MART-1 for treatment of metastatic melanoma. The presumed mechanism of autoimmune destruction of normal melanocytes in the stria vascularis of the cochlea and the vestibular end organs demonstrates the importance of melanocytes in inner ear function and provides insight into the pathogenesis of diseases such as VKH as well as other auto-immune diseases of the inner ear.

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Figure 1.

Potential cochlear insults prior to the initiation of adoptive cell immunotherapy (ACI). Prior ototoxic events include head or ear trauma ($n = 1$), cisplatin chemotherapy ($n = 2$), head or neck radiation treatment or exposure ($n = 3$), and loud noise exposure ($n = 10$). There was no significant relationship between prior ototoxic events and posttreatment change in hearing ($P = .48$). All patients with hearing loss prior to ACI demonstrated sensorineural hearing loss limited to the high frequencies. There was no significant relationship between the presence of a pre-ACI hearing loss and post-ACI treatment change in hearing ($P = .44$).

Figure 2.

Post-adoptive cell immunotherapy (ACI) hearing change by T cell dose. Post-ACI change in hearing level was strongly associated with higher doses of infused T cells ($P = .0001$). Data from both right and left ears are included for each patient. Trendline equation $y = 0.180x + 3.545$. R^2 value = 0.197. HL, hearing level.

Figure 3.

Hearing decline by number of T cells infused for adoptive cell immunotherapy (ACI). Post-ACI hearing decline was strongly associated with higher doses of infused T cells for ACI ($P < .0001$). The mean dose of cells infused for ACI was lowest in the group with no posttreatment change in hearing (13.3×10^9 ; range, $1.5\text{--}55.8 \times 10^9$). The dose was significantly higher in patients with a change in hearing resulting in a mild (59.1×10^9 ; range, $12.0\text{--}110.0 \times 10^9$; $P < .0001$) and moderate (63.3×10^9 ; range, $10.5\text{--}112.0 \times 10^9$; $P < .0001$) hearing loss. Note: Error bars represent standard error.

Figure 4.

Vestibular symptoms by number of T cells infused for adoptive cell immunotherapy (ACI). Vestibular symptoms were strongly associated with higher doses of infused T cells for ACI ($P = .007$). The mean dose for those without vestibular symptoms was 29.2×10^9 (range, $1.5\text{--}110.0 \times 10^9$), whereas the mean dose for patients with vestibular symptoms was 75.3×10^9 (range, $39.1\text{--}112.0 \times 10^9$). Note: Error bars represent standard error.

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Table 1.

Toxicities by ACI Dose

Patient	T Cells Infused for ACI (10 × 10 ⁶)	Baseline Hearing Status	Post-ACI Hearing Change	Hearing Recovery	Pre-ACI PTA, Right/Left, dB	Post-ACI PTA, Right/Left, dB	Final PTA Recovery, Right/ Left, dB	Post-ACI Vestibular Dysfunction	Objective Vestibular Recovery	Uveitis	Rash
1	1.5	Normal	No	—	5.0/3.8	*/5.0	*/5.0	No	—	No	Yes
2	1.8	Normal	No	—	12.5/18.8	10.0/18.8	10.0/18.8	No	—	No	Yes
3	2.0	Normal	No	—	12.5/13.8	11.3/13.8	11.3/13.8	No	—	No	Yes
4	2.3	Normal	No	—	5.0/6.3	3.8/6.3	3.8/6.3	No	—	No	No
5	2.7	Normal	No	—	7.5/6.3	8.8/6.3	8.8/6.3	No	—	No	Yes
6	4.8	Normal	No	—	2.5/2.5	2.5/2.5	2.5/2.5	No	—	No	No
7	5.9	Normal	No	—	12.5/11.3	12.5/15.0	12.5/15.0	No	—	Yes	No
8	6.5	Normal	No	—	6.3/16.3	8.8/16.3	8.8/16.3	No	—	Yes	Yes
9	9.8	Normal	No	—	11.3/10.0	11.3/12.5	11.3/12.5	No	—	No	Yes
10	9.8	Normal	No	—	11.3/10.0	11.3/12.5	11.3/12.5	No	—	No	Yes
11	9.9	Normal	No	—	13.8/15.0	15.0/17.5	15.0/17.5	No	—	No	No
12 ^a	10.5	Normal	Moderate	Yes	12.5/10.0	60.0/50.0	11.3/10.0	No	—	Yes	Yes
13	12.0	Normal	Mild	Yes	12.5/11.3	26.3/18.8	13.8/6.3	No	—	Yes	Yes
14	17.6	Mild HFSNHL	No	—	25.0/27.5	27.5/28.8	27.5/28.8	No	—	No	Yes
15	19.4	Normal	No	—	12.5/11.3	11.3/10.0	11.3/10.0	No	—	Yes	Yes
16 ^a	23.3	Mild HFSNHL	Mild	Yes	22.5/21.3	33.8/30.0	18.8/20.0	No	—	Yes	Yes
17 ^a	38.0	Normal	Moderate	Partial	12.5/8.8	63.8/61.3	35.0/31.3	No	—	Yes	No
18	39.1	Normal	Mild	Yes	10.0/8.8	21.3/18.8	8.8/10.0	Yes	Complete	No	Yes
19	46.5	Normal	Mild	Yes	6.3/8.8	28.8/33.8	7.5/10.0	No	—	Yes	Yes
20 ^a	48.2	Mild HFSNHL	Moderate	Partial	22.5/13.8	57.5/55.0	32.5/26.3	Yes	None	Yes	Yes
21	49.9	Normal	No	—	8.8/7.5	7.5/8.8	6.3/7.5	No	—	No	Yes
22	54.0	Normal	Mild	Yes	3.8/2.5	16.3/18.8	5.0/5.0	No	—	No	Yes
23 ^a	55.8	Normal	No	—	12.5/10.0	17.5/18.8	11.3/8.8	Yes	Complete	Yes	Yes
24	59.7	Normal	Mild	Partial	17.5/16.3	30.0/36.3	24.2/22.0	No	—	No	Yes
25 ^a	59.9	Normal	Mild	Yes	12.5/15.0	26.3/27.5	17.5/17.5	No	—	Yes	Yes

Patient	T Cells Infused for ACI (10 × 10 ⁶)	Baseline Hearing Status	Post-ACI Hearing Change	Hearing Recovery	Pre-ACI PTA, Right/Left, dB	Post-ACI PTA, Right/Left, dB	Final PTA Recovery, Right/ Left, dB	Post-ACI Vestibular Dysfunction	Objective Vestibular Recovery	Uveitis	Rash
26 ^a	68.0	Normal	Moderate	Partial	17.5/12.5	43.8/43.8	17.5/18.8	Yes	None—subjectively improved	Yes	Yes
27 ^a	73.0	Normal	Moderate	Yes	8.8/10.0	37.5/33.8	12.5/15.0	No	—	Yes	Yes
28	80.0	Normal	Mild	Yes	13.8/13.8	23.8/22.5	13.8/11.3	No	—	Yes	No
29	94.1	Mild HFSNHL	Moderate	Yes	32.5/36.3	41.3/46.3	26.3/30.0	Yes	Partial	No	Yes
30	110.0	Normal	Mild	Yes	5.0/7.5	16.3/17.5	5.0/11.3	Yes	None—subjectively improved	No	Yes
31 ^a	110.0	Normal	Moderate	Yes	17.5/18.8	42.5/41.3	20.0/26.3	No	—	Yes	Yes
32 ^a	112.0	Normal	Moderate	Partial	5.0/3.8	50.0/52.5	22.5/20.0	Yes	Complete	Yes	Yes

Posttreatment decline in hearing and vestibular dysfunction was more common in those patients receiving higher numbers of T cells infused for adoptive cell immunotherapy (ACI) treatment ($P < .0001$ and $P = .007$, respectively). Baseline hearing levels are included, as well as post-ACI hearing level and recovery. Hearing levels are reported in decibels hearing level (dBHL) as 4-tone pure-tone average (PTA) for 500, 1000, 2000, and 4000 Hz. Associated toxicities were also noted. Twenty-six patients developed a rash after treatment with ACI, and 15 (57.7%) of these also had posttreatment change in hearing sensitivity. Of the 6 patients without rash, 2 (33%) had hearing loss. The presence of rash did not correlate with posttreatment change in hearing ($P = .38$). Uveitis was noted in 16 patients, 12 (75.0%) of whom had post-ACI hearing loss. In those patients who did not develop uveitis ($n = 16$), only 5 (31.3%) had changes in hearing. Uveitis was statistically correlated with post-ACI hearing decline ($P = .03$). HFSNHL, high-frequency sensorineural hearing loss. Dashes indicate data not applicable. Asterisks indicate no data available.

^aPatients who received intratympanic steroid injections.