



Sensorineural hearing loss in a patient with follicular lymphoma treated with bendamustine and rituximab

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Abstract: Bendamustine-rituximab is being increasingly used in the treatment of indolent non-Hodgkin's lymphoma, both first line and in cases of relapsed or refractory disease. We report a case of bendamustine associated sensorineural hearing loss in a 41-year-old lady with follicular lymphoma. A correlation between bendamustine and ototoxicity, in a patient with previously normal hearing, has not been demonstrated within the literature. However, there is significant evidence of ototoxicity and neurotoxicity caused by other alkylating agent and purine analogue drugs and there is growing evidence for the role of bendamustine in the development of neurotoxicity. As such, the development of neurologic sequelae in any patient receiving bendamustine therapy should prompt urgent review of the ongoing chemotherapy regime.

Keywords: Non-Hodgkin's lymphoma; bendamustine; sensorineural hearing loss

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Introduction

Bendamustine is composed of an alkylating agent with a benzimidazole ring and a butyric acid side chain (1,2). Due to its chemical structure, bendamustine has alkylating agent properties, with only partial cross-resistance to other alkylating agents (2), purine analogue activity and acts synergistically with other chemotherapeutic agents (3). The precise mechanism of action remains largely unknown (3), however, it is hypothesized to stimulate apoptosis, induce mitotic catastrophe, inhibit mitotic checkpoints and induce DNA damage (2).

Bendamustine-rituximab (BR) is a widely accepted treatment for indolent B cell malignancies, both as first line treatment and in cases of relapsed or refractory disease (1,2,4). In clinical trials, several groups of investigators have demonstrated BR to be effective and generally well tolerated (1,5). The most common side effects are myelosuppression, gastrointestinal events, infection, fatigue, hypersensitivity reactions and erythematous skin

reactions (6). Although purine analogues and alkylating agents have been associated with neurotoxicity (7-9), bendamustine (as a monotherapy or in combinations) has not been reported to cause ototoxicity in patients with previously normal hearing.

Case presentation

A 41-year-old female, with a medical history of amenorrhea and hypothyroidism, presented with central back pain. Imaging investigations demonstrated bulky retroperitoneal lymphadenopathy and laparoscopic biopsy of the tissue yielded a diagnosis of follicular lymphoma, WHO grade 3A. Bone marrow biopsy confirmed low volume involvement with lymphoma (stage IVA) and the follicular lymphoma international prognostic index was 1 (low risk). Treatment with BR was initiated at a standard dose of bendamustine (90 mg/m²). Aside from ongoing symptoms of headache and nausea, not associated with other neurological symptoms or signs, the first three cycles were well tolerated. The fourth

cycle was complicated by an episode of non-neutropenic sepsis requiring admission to the high dependency unit for inotropic support. The source of the infection was not determined, all imaging and microbiological investigations were unremarkable, but the patient responded to piperacillin-tazobactam, which was stepped-down to amoxicillin/clavulanate on discharge from hospital.

Immediately following this hospital admission, the patient first noticed symptoms of right-sided hearing loss associated with aural fullness and tinnitus. These symptoms were reported two weeks later and immediate audiometric evaluation confirmed a unilateral right-sided sensorineural hearing loss (SNHL). Cranial nerve, neurological, head impulse and otoscopic examinations were unremarkable. Tuning fork assessment revealed lateralization to the left on the Weber test and a Rinne test that was positive bilaterally. Tympanometry demonstrated a type A(d) tympanogram bilaterally and audiometry revealed a mild-moderate high frequency hearing loss on the right, sensorineural in pattern, and mild hearing loss on the left, more consistent with previous sound induced hearing loss (*Figure 1A*). A provisional diagnosis of right-sided idiopathic SNHL was made, and a 10-day course of prednisolone 50 mg was completed.

Cycle five of BR started without dose alteration. This was complicated by neutropenic sepsis, again requiring HDU admission for inotropes. Piperacillin-tazobactam 4.5 grams was given eight hourly and, due to refractory hypotension, one dose of gentamicin 4 mg/kg followed by vancomycin 1.5 grams (12 hourly for three doses). Again, no source of infection was found despite imaging and microbiological investigations. She recovered well from the sepsis, however, during the admission the right-sided hearing loss dramatically worsened and progressed to bilateral hearing loss. Subsequent hearing assessment confirmed a mild-moderate bilateral SNHL on audiogram (*Figure 1B* below) and type A(d) tympanograms. Magnetic resonance imaging of the posterior fossa did not demonstrate pathology to account for the symptoms. Baseline bloods tests, including antinuclear antibodies, anti-Rhodopsin antibodies and anti-double-stranded DNA antibodies were negative. Intra-tympanic steroids were trialed with minimal benefit. A provisional diagnosis of chemotherapy related, steroid non-responsive hearing loss was made.

End of treatment positron emission tomography with computer tomography scan demonstrated complete metabolic remission and she remained in clinical remission at six-month follow-up from end of treatment. However,

the hearing loss had progressed and continued to affect quality of life. She reported difficulty hearing in noisy rooms, necessitating lip reading. At eight months post treatment her hearing threshold remained within a range that could be rehabilitated by way of conventional hearing aids, at which time she was referred to an audiologist for assessment. However, at twelve months post treatment, her hearing has improved, hearing aids are no longer required and she is awaiting further audiometric evaluation.

Discussion

Although bendamustine is generally well-tolerated (1), the temporal association (first episode of SNHL occurring four weeks prior to exposure to ototoxic antibiotics) is suggestive of bendamustine-related SNHL. However, it is likely that antibiotic therapy was an exacerbating factor as, post-onset of SNHL, the patient received doses of potentially ototoxic antibiotics (vancomycin and gentamicin). The only antibiotic received prior to development of the SNHL was Piperacillin-Tazobactam. We are unaware of any literature suggesting a correlation between penicillin/ beta-lactam antibiotics and ototoxicity. Aminoglycosides, such as gentamicin, are well known to cause irreversible cochlea toxicity and permanent SNHL (10). Glycopeptides, such as vancomycin, have been associated with ototoxicity, however, causality remains somewhat uncertain and ototoxicity was not observed at therapeutic doses in more recent clinical trials (10). Therefore, we hypothesize bendamustine to be a contributor to SNHL in this patient, with gentamicin a likely exacerbating factor.

Sensorineural hearing loss, of a toxic etiology, is commonly bilateral and symmetrical (11). However, there is substantial evidence within the literature which demonstrates that unilateral ototoxicity can result from both platinum based chemotherapy (11,12) and aminoglycoside antibiotics (13). A more recent study by Chauhan and colleagues (14) proposed that ototoxicity might in fact be unilateral before it is bilateral, a finding which could prompt alteration of the treatment regime to prevent progression to a bilateral hearing loss. The above findings are consistent with those of this case report, an initial unilateral ototoxicity that progressed to bilateral ototoxicity with further bendamustine therapy +/- one dose of gentamicin antibiotic.

We identified one prior case of bendamustine associated hearing loss (15). Bergmann *et al.* reported marked worsening of hypacusis in a patient with chronic

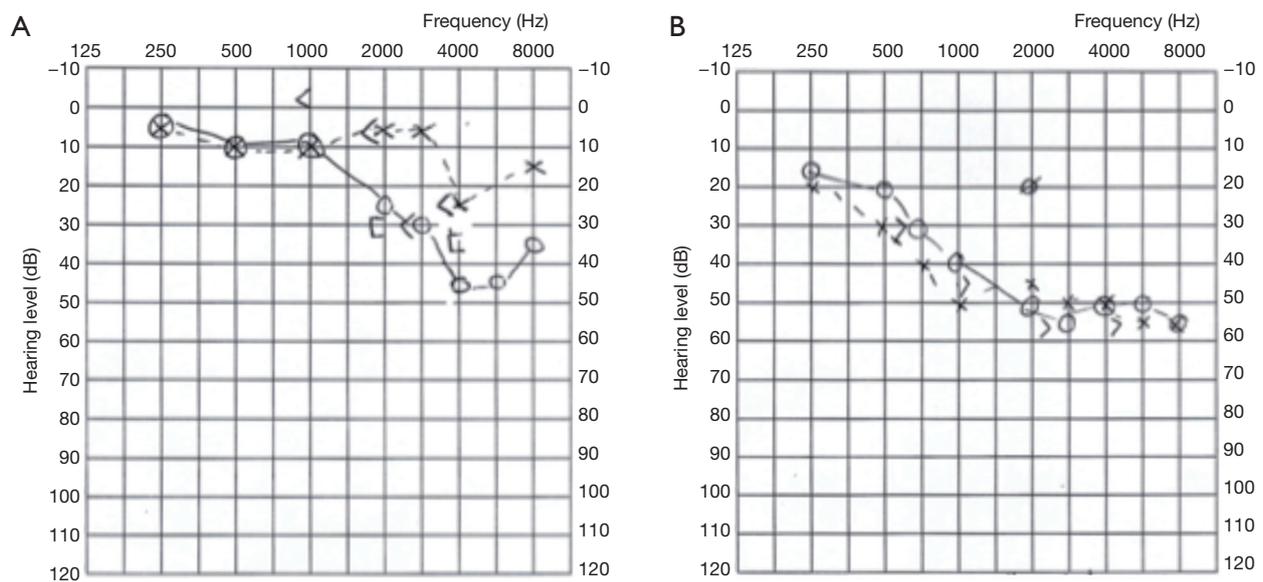


Figure 1 Patient audiograms. Audiograms demonstrating hearing level at various frequencies. The circle (O) represents air conduction and the less than symbol (<) bone conduction in the right ear. The cross (X) represents air conduction and the greater than symbol (>) bone conduction in the left ear. (A) represents the first audiogram conducted on the (30/11/17). Hearing level is seen to decrease with higher frequencies, worse in the right ear than the left. (B) represents the audiogram conducted after the second episode of sepsis and exposure to ototoxic antibiotics (10/01/18). Hearing level is seen to decrease at higher frequencies in both right and left ears.

lymphocytic leukemia and pre-existing hearing loss, following bendamustine monotherapy. We are unaware of any reports of bendamustine associated ototoxicity in patients with previously normal hearing. Although there are no reports of bendamustine induced cranial neuropathy, there are numerous reports of bendamustine associated peripheral neuropathy (5,7,8,15). Cheson and Kroll (7) and Alhafez *et al.* (8) reported two separate cases of rapidly ascending neuropathy, and associated neurologic sequelae, in patients with lymphoma treated with BR. In both cases no other etiology was identified and the neuropathy was minimally responsive to steroid therapy.

Alkylating agents are known to cause irreversible ototoxicity (10,16,17). Platinum agents (e.g., cisplatin) are well known to cause SNHL and associated tinnitus and vertigo (10,17). Risk factors for cisplatin ototoxicity include the level of an individual single dose, cumulative dose and pre-existing hearing impairment or renal insufficiency (10). The proposed mechanisms of action are via double stranded DNA damage as well as production of reactive oxygen species, which accumulate in the mitochondria, upset oxidative metabolism and cause progressive damage to strial marginal cells and cochlea hair cells (17,18). Reports of purine analogue associated ototoxicity are lacking,

however, these drugs have been associated with significant neurotoxicity (9), the mechanism of which is unknown but could relate to the benzimidazole structure or other immunosuppressive effects (9). As bendamustine has both alkylating agent and purine analogue moieties, it is possible that it could exert ototoxic or neurotoxic effects in a similar manner to these agents.

This is the first report, to our knowledge, of bendamustine induced SNHL in a patient with previously normal hearing. Although, gentamicin was likely an exacerbating factor. Given that one of the primary reasons to use BR over alternate regimens is the favorable toxicity profile, clinicians should be aware of bendamustine associated SNHL. The development of SNHL in a patient receiving bendamustine therapy should prompt urgent Otolaryngology referral and avoidance of further bendamustine exposure.

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Footnote

Conflicts of Interest: G Rule and A Esmaili report no conflicts

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Informed Consent: Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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