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LETTER TO THE EDITOR

Brentuximab vedotin-induced peripheral neuropathy: looking at microtubules

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To the Editor,

We read with interest the article by Corbin et al. on the characterization of treatment-emergent peripheral neuropathy (PN) in patients with mycosis fungoides and Sézary syndrome (MF/SS) receiving brentuximab vedotin (BV), recently published in your journal [1]. In this phase II study, BV was administered intravenously at doses of 1.8 mg/kg, every three weeks for up to eight cycles, to MF/SS patients, who previously failed at least one systemic therapy. BV doses were delayed or reduced in patients developing grade 2 PN and discontinued with grade 3 PN.

As compared to available literature on BV-related PN in patients with Hodgkin lymphoma and systemic anaplastic large-cell lymphoma, Corbin et al. observed a higher rate of PN, a shorter median time to grade-2 neuropathy, and a longer median time to improvement or resolution after the last BV dose [1]. To assess and grade PN the authors used the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0, and the Total Neuropathy Score clinical version (TNSc), which are validated composite scales, not inclusive, however, of nerve conduction studies. Since PN is the main adverse effect of BV responsible for dose modifications, treatment delays or discontinuations, this focused study is of major interest, although some points need further discussion.

It is unclear why some patients with grade 1 neuropathy (see Fig. 1a from the top, bar 5, 6, 11), in addition to a patient with no neuropathy (bar 22), had end of treatment before completing the eight cycles. Moreover, the inclusion of patients with pre-existing neuropathy at study entry may represent a confounding factor and introduces bias in the characterization of BV-associated neuropathy. Based on our experience, many patients who are candidates to BV treatment have a subclinical/grade 1 PN, due to prior exposure to other neurotoxic agents, which predispose and increase the risk of developing PN after the start of BV treatment; likewise, some patients may have an underlying neuropathy, either related to the hematologic disorder itself, or secondary to other common comorbidities. An example of the occurrence of this circumstance is outlined by Corbin et al. as worsening of PN in 7 out of 9 subjects with baseline clinically-defined PN. Taken together, the role of neurophysiological investigations in detecting subclinical PN and in characterising the involvement of peripheral nerves, whether axonal or demyelinating, has to be underlined. In this study, among the 5 reported neurophysiological studies in 4 symptomatic patients, one patient had a demyelinating neuropathy, suggested to be of genetic origin, although the observed short-term progressive features stand against a hereditary neuropathy, where no major appreciable conduction velocity changes are expected as the disease progresses. In addition, 2 patients showed a more typical length-dependent axonal pattern, which rules out the occurrence of a dorsal root ganglionopathy, whereas the latter patient had an atypical patchy involvement. These findings suggest that electrodiagnostic work-up is also fundamental in detecting focal neuropathy and in monitoring changes in the severity of peripheral nerve damage. Finally, Corbin et al. obtained a sural nerve biopsy in a patient with grade 4 PN, presenting with numbness and weakness, a finding consistent with previous evidence of motor involvement in 11% of BV-treated patients [2]. Observed neuropathological changes consisted in mild loss of myelinated fibers in the absence of CD30-expressing cells or cellular inflammation. Therefore, it is argued that the patient had a predominantly motor axonal neuropathy, owing to the mild axonal loss detected in a sensory nerve.

Axonal pathology is a feature encountered in patients treated with drugs causing polymerization of microtubules and blocking their depolymerisation, such as taxanes, as well as with antineoplastic agents promoting microtubule

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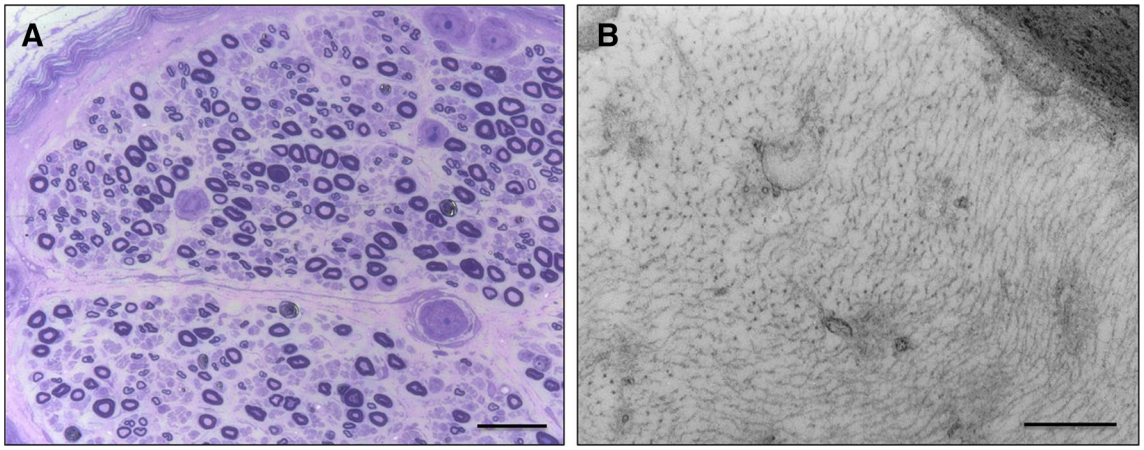

Fig. 1 **a** Spurr-embedded cross section of the sural nerve (toluidine blue stain) of a patient with BV-related neuropathy shows reduced density of myelinated fibers, ongoing wallerian-like degeneration, and regenerating clusters (scale bar = 50 µm). **b** Electron micrograph of a myelinated axon showing marked depletion of axonal microtubules and bundles of misaligned, cross-oriented neurofilaments (scale bar = 300 nm)

disassembly or blocking their polymerization, such as Vinca alkaloids and monomethyl auristatin E. More recent studies have confirmed the high rates of BV-induced peripheral neuropathy reported by Corbin et al., showing an incidence of 83% in patients with benign forms of cutaneous lymphoproliferative disorders, such as lymphomatoid papulosis [3], and of 67% in patients with CD30-positive mycosis fungoides or primary cutaneous anaplastic large-cell lymphoma [4].

To date, while an alteration of axonal microtubules has been claimed as the possible cause of fast axonal transport derangement, no consistent proof has been replicated in BV-treated patients, following our previous observation [5], showing severe microtubule loss, disorganization of axonal cytoskeleton, and focal accumulation of smooth endoplasmic reticulum and membranous organelles (Fig. 1). Obviously, the detection of the aforementioned changes requires electron microscopic examination. Neuronal microtubules and their associated motor proteins are fundamental in driving long-range intracellular transport in neurons and their axonal and dendritic extensions. Intriguingly, defects in microtubule-dependent transport are observed in genetic neurologic conditions affecting tubulin and motor proteins, such as hereditary spastic paraplegia, Charcot–Marie–Tooth disease, axonal sensorimotor neuropathy, and progressive motor neuropathy. As such, PNs induced by drugs stabilizing microtubules or promoting microtubule disassembly might share common molecular mechanisms with genetic neurological conditions.

Compliance with ethical standards

Conflict of interest The authors have nothing to disclose.

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