

Tubulin involvement in Bortezomib peripheral neurotoxicity

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Axonal transport of mitochondria (Mt) controlled by specialized motor and docking proteins that distribute Mt throughout the axon where they provide energy for metabolic and synaptic activity is a vulnerable target in neuronal pathology (1). Bortezomib (BZ) is a proteasome inhibitor active in multiple myeloma (2). One of its key toxicities is painful peripheral neuropathy (BIPN), which frequently requires treatment discontinuation (3). BIPN is dose-related and predominantly sensory, resulting from axonal degeneration. Recent results indicate that BZ modifies axonal tubulin dynamic and we hypothesize that BZ alters fast axonal transport. Here we studied using time-lapse imaging the effect of different BZ concentration on axonal Mt transport in isolated dorsal root ganglion (DRG) neurons from adult male mice. We used kymograph to quantify the total number of Mt and to discriminate antero and retrogradely moving Mt from stationary Mt. Twenty-four hours of BZ treatment (0.1 to 15 μ M) induced a dose-dependent reduction in Mt trafficking. Moreover, BZ had no impact on MT motion directions, but it induced a progressive reduction of both anterograde and retrograde axonal transport velocities. These events were associated with increase in tubulin polymerization and of MAP2 expression, but they occurred only after 72h of chronic BZ treatment. We have developed an in vitro model of BIPN demonstrating that transport impairment is already present before evident tubulin polymerization, suggesting that transport deficit represents an early stage of axonal dysfunction. Perpetuated transport dysfunction could impair distal organelle supply and play a critical role in advanced stages of BIPN.

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References

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Keywords

Bortezomib; peripheral neuropathy; mitochondrial trafficking; adult DRG sensory neurons; mice.