Bortezomib attenuates HIF-1- but not HIF-2-mediated transcriptional activation

ABSTRACT

Bortezomib is the first proteasomal inhibitor (PI) to be used therapeutically for treating relapse cases of multiple myeloma and mantle cell lymphoma. A proposed mechanism for its action is that it prevents the proteasomal degradation of proapoptotic proteins, leading to enhanced apoptosis. Although the α subunit of hypoxia‐inducible factor (HIF)‐1 is not degraded with bortezomib treatment, the heterodimeric HIF‐1 fails to transactivate target genes. HIF‐1 and HIF‐2 are related hypoxia‐inducible transcription factors that are important for the survival of hypoxic tumor cells. The majority of reports have focused on the effects of bortezomib on the transcriptional activities of HIF‐1, but not HIF‐2. The present study investigated the effects of bortezomib on HIF‐2 activity in cancer cells with different levels of HIF‐1α and HIF‐2α subunits. HIF‐α subunit levels were detected using specific antibodies, while HIF transcriptional activities were evaluated using immunodetection, reverse transcription‐polymerase chain reaction and luciferase reporter assay. Bortezomib treatment was found to suppress the transcription and expression of CA9, a HIF‐1‐specific target gene; however, it had minimal effects on EPO and GLUT‐1, which are target genes of both HIF‐1 and HIF‐2. These data suggest that bortezomib attenuates the transcriptional activity only of HIF‐1, and not HIF‐2. This novel finding on the lack of an inhibitory effect of bortezomib on HIF‐2 transcriptional activity has implications for the improvement of design and treatment modalities of bortezomib and other PI drugs.

Keyword: Bortezomib; Hypoxia-inducible factor; HIF-1; HIF-2; Transcriptional activity