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Endothelin Signaling as Target for Anticancer Therapy: from Prostate Cancer to Multiple Myeloma

* Panagiotis J. Vlachostergios
Division of Hematology and Medical Oncology, Weill Cornell Medicine, New York, NY, USA

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*For Correspondence

Panagiotis J. Vlachostergios
Division of Hematology and Medical Oncology, Weill Cornell Medicine, New York, NY, USA

Email: pjv9003@nyp.org
Contact no: 646 962 2357
Fax no: 646 962 0115

Neuropeptides including endothelin 1 (ET-1) are potent mitogens for both benign and malignant cells through G-protein receptor binding and signal transduction \[^1\]. Aberrant expression of several components of the endothelin axis, including ET-1 and its receptors, ET-A and ET-B is found in various malignancies, including prostate cancer (PC) \[^1\]. Evidence of increased paracrine and autocrine signaling through the endothelin axis in PC cells has triggered clinical testing of ET-1 receptor inhibitors. However, lack of clinical benefit has prevented further development of this approach \[^2\]-\[^5\]. At the cellular level, we previously reported ET-induced upregulation of proteasome activity and associated proliferative and antiapoptotic effects in androgen-independent PC cells \[^6\]. These effects were reversed with the use of the proteasome inhibitor bortezomib \[^7\]. However, bortezomib failed to demonstrate clinical activity in PC patients, thus its clinical use for inhibiting the endothelin axis could not be supported in that setting \[^8\]-\[^11\].

Nonetheless, in multiple myeloma (MM) bortezomib is a very active drug and often consists the backbone for most myeloma treatment regimens \[^12\]-\[^14\]. We have previously revealed the overexpression of ET-B in MM mediating resistance to bortezomib via upregulation of proteasome activity and resultant MAPK pathway activation \[^15\]. In their recent work, published in the British Journal of Haematology, Russignan et al. further complemented these findings by reporting ET-B overexpression in human malignant plasma cells compared to healthy donors \[^16\]. Moreover, the addition of an ET-1 receptor antagonist to bortezomib enhanced the cytotoxic effect on myeloma cells \[^15, 16\].

In summary, the rational for ET-1 receptor antagonism in myeloma has been documented. Therefore, design and conduction of a clinical trial combining bortezomib and a non-selective ET-1 receptor antagonist, for example bosentan, or a selective ET-B receptor antagonist, appears to be a reasonable next step and holds promise for further improving outcomes of MM patients.

**REFERENCES**


