



Sculpture of Skeleton--Oggiaro, Milan

## PIC QUESTION OF THE WEEK: 2/07/11

Q: Why is valproic acid being investigated for use in patients with multiple myeloma?

A: Multiple myeloma (MM) is an incurable malignancy of B-cells characterized by infiltration of malignant *plasma cells* into the bone marrow resulting in eventual bone destruction. MM cells enhance osteoclastogenesis, stimulate angiogenesis, and suppress formation of osteoblasts leading to rapid loss of bone, thus enhancing the microenvironment and permitting accumulation of large numbers of malignant cells within the marrow. Anti-myeloma treatment must not only target myeloma cells, but also reduce the area within the marrow that is available for their penetration. Currently, MM is treated with anthracyclines, vinca alkaloids, and dexamethasone-based regimens and often followed by autologous bone marrow transplantation. Newer therapies include thalidomide, bortezomib, and lenalidomide. Compounds known as histone deacetylase (HDAC) inhibitors preserve the acetyl groups on histones and decrease their positive charge. DNA interacts to a lesser degree with this type of histone and various transcription factors, thus resulting in altered gene expression and anti-tumor effects. Previously studied compounds with HDAC inhibitory activity have already been proven to trigger cell growth inhibition, cell cycle arrest, and MM cell apoptosis and potentially hold promise because they act preferentially on malignant cells. Valproic acid (VA) is generally a well tolerated anticonvulsant and also known to be an HDAC inhibitor. Because of this activity, VA has generated some enthusiasm for a potential role in the treatment of MM. VA is thought to exert anti-tumor effects through several heterogeneous mechanisms. Results of *in vitro* studies indicate that VA induces both anti-proliferative activity against MM cell lines and apoptosis. In addition, *in vivo* studies reveal that VA modulates the cell cycle resulting in inhibition of tumor growth and a significant increase in survival. VA's effects on gene expression result in several anti-tumor properties. Genes involved in DNA replication, RNA splicing, transcriptional regulation, cell proliferation, and negative regulation of apoptosis are *downregulated*, while those associated with negative regulation of cell growth and oncosuppression are *upregulated*. Finally, VA can affect the microenvironment by suppressing osteoclastogenesis and angiogenesis while enhancing osteoblast differentiation. Although clinical trials have yet to be conducted, valproic acid appears to possess promise as a supplementary agent in the treatment of multiple myeloma.

### References

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