Scientific & Clinical

The role of vorinostat in relapsed/refractory multiple myeloma

Myeloma Today in conversation with Prof. Meletios A. Dimopoulos

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How do you define "relapsed" and "refractory" multiple myeloma?

I define relapse as the presence of clinically active disease in patients who have received one or more prior therapies. Refractory multiple myeloma can be defined as either progressive disease (PD) or stable disease (SD) while on therapy, or PD within 3 months of the last dose of prior therapy.

What are the challenges of treating relapsed or refractory myeloma?

Patients with relapsed/refractory myeloma can be categorized as following: patients who are refractory to frontline therapies, patients who have relapsed but who are not refractory to treatment, and patients who are both relapsed and refractory. Newly-diagnosed myeloma is usually responsive to initial treatment. However, most patients with this disease eventually relapse or become not readily responsive to currently available anti-myeloma agents. This is due in part to the evolving biology of myeloma and/or the development of drug-resistance within the cancer cells.

What are the currently-available treatment options for relapsed/refractory disease?

Currently, three novel agents are approved in most countries for the treatment of myeloma as frontline therapy and/or in the relapsed/refractory setting: thalidomide (THALOMID®), lenalidomide (REVLIMID®), and bortezomib (VELCADE®). These novel agents are used in frontline therapy and can provide clinical benefit in relapsed/refractory disease. But not all relapsed/refractory patients will respond to currently approved drugs, and the responses can be limited in duration. For patients with relapsed myeloma who are refractory to these agents, there is an urgent need to develop targeted agents that provide durable disease control and symptomatic relief.

Please give us a brief overview of the targeted agents that are currently under investigation for myeloma.

The progress being made in the treatment of relapsed/refractory myeloma is encouraging. Several new

agents from a range of therapeutic classes and with varied rationales for use in myeloma are showing potential to provide improvements in response and survival in the relapsed/refractory setting. Agents in development for the treatment of bortezomib- or lenalidomide-resistant myeloma include pomalidomide, carfilzomib, perifosine, elotuzumab, and several histone deacetylase (HDAC) inhibitors (e.g., panobinostat, romidepsin, and vorinostat). Completion of the numerous ongoing clinical investigations should determine which, if any, of these newly emerging therapies are viable treatment options for patients with relapsed/refractory myeloma.

You have been involved with studies of vorinostat for relapsed/refractory myeloma. Please tell us about this compound and its development history.

HDAC inhibition may play a critical role in controlling tumor growth and increasing survival. Vorinostat (suberoylanilide hydroxamic acid) is an oral HDAC inhibitor that has been developed for the treatment of several malignancies. In 2006, vorinostat was approved in the United States for the treatment of patients with cutaneous T-cell lymphoma who have progressive, persistent, or recurrent disease on or following two systemic therapies. The safety and tolerability of vorinostat has been well-documented both in patients with hematologic malignancies and those with solid tumors. Preliminary studies of vorinostat in patients with relapsed/refractory myeloma did not show significant single-agent activity, but there was a significant in vitro rationale to combine vorinostat with either bortezomib or lenalidomide.

What was that rationale?

Preclinical data of vorinostat in myeloma showed that it has antiproliferative/proapoptotic activity against human myeloma cells, overcomes the protective effect of bone marrow stromal cells on myeloma cells, and enhances the response of myeloma cells to other antimyeloma compounds. The data from the preclinical studies provided the “proof of concept” that led to the development of clinical trials to further explore the activity of this compound in myeloma.

VANTAGE 074, a phase I multicenter, open-label study of vorinostat, lenalidomide, and dexamethasone for relapsed/refractory myeloma aimed to determine the maximum tolerated dose (MTD) for that three-drug combination regimen. Most study patients received prior therapy with bortezomib, thalidomide, and/or lenalidomide. Based on April 2010 preliminary data, 26 of 30 patients evaluable for efficacy (86.7%) had clinical benefit: complete response (CR) + partial response (PR) + minimal response (MR) + stable disease (SD) on treatment. In addition, data showed that MTD has not been reached, with no dose-limiting toxicities (DLT) prohibiting dose escalation. This suggests that vorinostat combined with lenalidomide and dexamethasone may be an effective and generally well-tolerated oral regimen for patients with relapsed/relapsed myeloma. Further data collection and review are ongoing, and a phase II study is planned.

Indeed, the phase I and II clinical studies of vorinostat in myeloma showed interesting activity indicating that there was clinical synergy between vorinostat and bortezomib, as well as vorinostat and lenalidomide. Investigation of vorinostat plus lenalidomide has been presented at recent annual meeting of the American

Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO), and the European Hematology Association (EHA). Vorinostat was shown to have activity in heavily pretreated myeloma patients and in those who are refractory to bortezomib and lenalidomide.

What are the significant ongoing clinical trials?

At present, there are two major clinical trials of vorinostat. One of these trials – VANTAGE 095 – is a large phase IIb international open-label single-arm study designed to assess efficacy and safety of treatment with vorinostat plus bortezomib in patients who are refractory to bortezomib and ≥1 immunomodulatory drug (IMiD) regimens and are ineligible for other approved regimens. Such patients are known to have very poor outcomes, with a median survival of 6 months or less, so this trial is very important in attempting to address a currently unmet need.

The second major ongoing clinical trial of vorinostat is VANTAGE 088, a phase III multi-center randomized double-blind study of vorinostat or placebo combined with bortezomib in relapsed myeloma. The primary objective of this study is to determine the progression-free survival (PFS) of vorinostat plus bortezomib, compared with placebo plus bortezomib, in myeloma patients who had received between one and three prior treatment regimens. The patients being accepted into this study must not be refractory to bortezomib.

Are you involved with both of the currently ongoing clinical trials?

Yes, I am working on both VANTAGE 088 and VANTAGE 095 as a member of the steering committee. The VANTAGE trial is the largest clinical study for myeloma, enrolling 742 patients at 265 sites in 32 countries throughout the world VANTAGE 088 should conclude the accrual process within the next year. VANTAGE 095 is closer to completion of the patient accrual process, and we should have a formal interim analysis completed by the end of this year.

We do not yet have the final response data from the VANTAGE 095 study, but the preliminary data show that vorinostat has activity in myeloma. This is rather interesting, especially considering that this data comes from a heavily pretreated patient population. Of course, we have to wait until this study is fully accrued. But, hopefully, we will continue to see induced responses in 20-30% of participating patients who have disease which is otherwise refractory to all types of standard treatments. We have submitted an abstract to ASH 2010, and it is now under review.

What is your assessment of vorinostat so far?

I think that vorinostat is a very interesting compound. So far, the safety of the compound is looking reasonable, and we hope that the data will also show positive efficacy. Of course, patients receiving vorinostat require close follow-up, and might require dose adjustment, because it is associated with gastro-intestinal toxicity, a sense of weakness and fatigue. However, the combination of vorinostat with either bortezomib or lenalidomide has been shown to be generally well-tolerated.

Some study patients with resistant myeloma, for whom there are no other available treatment options, are showing some response from vorinostat plus bortezomib. So VANTAGE 088 and VANTAGE 095 are both very important clinical trials. We are looking forward to their completion, as there is a reasonable hope that the results of these trials may lead to a new treatment option being approved for patients with advanced myeloma.