

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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New Therapies for the Treatment of Multiple Myeloma

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H&O What new understandings have been reached regarding multiple myeloma?

PR Several key observations have been made. Perhaps the most important of these is that the multiple myeloma (MM) tumor microenvironment, and in particular the interaction between the myeloma cell and its stroma in the marrow, together with the new vessels that support its growth and other components of the marrow milieu and matrix, are key to the way that MM cells can both grow and survive. This interaction is key for MM to resist stress from standard chemotherapeutic agents and other forms of treatment, such as radiation. In my view, the recognition that the marrow microenvironment in MM is a vital target has been one of the most important steps in developing new treatment paradigms for the disease.

The specifics of these observations are complex. There are a series of signal transduction pathways that are controlled by the interaction between MM and the stroma. Growth factors produced by adherent stroma promote MM cell growth and survival, as do direct ligand interactions between the myeloma cell surface and the stroma. Also, there are direct and indirect interactions that modulate new vessel formation, and there are interactions through the production of cytokines (such as transforming growth factor β and other immunomodulators) that can suppress the ability of the patient's immune system to recognize and kill MM. The understanding of the complexity of these mechanisms has led to the opportunity to develop drugs that target both the tumor cell and the microenvironment.

H&O What new therapies have been developed in accordance with these understandings?

PR A seminal observation was that the ubiquitin pathway was critical for protein degradation in eukaryotic cells, and that the proteasome was a vital part of this pathway. The proteasome inhibitors were developed based on these observations. The first clinically usable agent in this class is a boronic acid-derivative dipeptide, bortezomib (Velcade, Millennium), a reversible inhibitor of the proteasome. Bortezomib targets numerous pathways, primarily by inhibiting the proteasome and controlling key transcription factors like nuclear factor κ -B (NF κ B). Also, bortezomib kills MM directly, disrupts the pathways of adhesion between MM and the stroma, blocks the production of MM "miracle grow" from the adherent stroma—including cytokines such as tumor necrosis factor alpha, interleukin-6 and interleukin-1—and blocks new vessel formation by inhibiting vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and perhaps through direct effects on activated endothelium.

Thalidomide (Thalomid, Celgene) accomplishes similar antitumor effects as bortezomib in MM, but via different pathways. Thalidomide is also an immunomodulator, which upregulates the immune system and triggers the upregulation of key T cells that fight myeloma directly. The thalidomide analog lenalidomide (Revlimid, Celgene) is a more potent form of thalidomide, and without the same array of side effects. Pivotal phase III studies have recently confirmed the activity of lenalidomide, and results of these trials will be presented at this year's annual meeting of the American Society of Clinical Oncology. In aggregate, they will demonstrate that lenalidomide represents the next major advance in the treatment of MM.

Presently, bortezomib, lenalidomide, and thalidomide constitute the 3 most important new agents for the treatment of MM. By combining standard chemotherapy (CT) with these drugs, the therapeutic index appears to be enhanced, including for patients who have been resistant to such therapies when used alone. Indeed, the integration of these new treatments is providing an opportunity to improving the outcomes derived from transplant, which hitherto had provided the biggest improvement in outcome for patients able to undergo it.

For example, if a patient has already received thalidomide, and their disease has progressed, and then the same patient has benefited from bortezomib-based therapy but become resistant, these 2 agents can be combined and dexamethasone added, with a response to the combination being likely. Most recently, this effect has been demonstrated with lenalidomide plus bortezomib.

H&O With so many options now available, is it possible to identify which patients are likely to benefit from one therapy or another?

PR Genomics are being performed in an exploratory fashion in order to better characterize disease, so that we know better what particular molecular and genetic profiles predict for responsiveness to certain therapies in MM. Preliminary data have identified certain gene marker sets that are associated with greater responsiveness to bortezomib, as opposed to nonresponse. These findings provided a rationale for bringing in other novel therapies currently being explored. There are drugs that target heat shock protein (HSP)-90, an important molecular chaperone that is upregulated by cancer cells, including MM, in response to bortezomib and other stresses. Thus one could hypothesize that by bringing these 2 agents together—the HSP-90 inhibitor and bortezomib—resistance to the latter agent could be overcome. Indeed, preclinical models have suggested this to be true, and now the concept is being tested in phase I studies. Other examples include a drug that inhibits a key growth factor, FGF receptor 3 (FGFR3), which is coded for by the t4,14 chromosomal translocation found in a subgroup of MM patients. This patient subgroup tends to have disease that is difficult to treat and does not respond particularly well to CT. This drug is about to enter a phase I clinical trial in MM.

H&O What other pathways are being pursued in the treatment of MM?

PR A long list of pathways are being explored, not only in the MM cell itself but also in the tumor microenvironment. This latter area of research is exciting and holds promise for enhancing already effective treatments of MM and reducing toxicity. Drugs in this class, including a p38 mitogen-activated protein (MAP) kinase inhibitor, SC-469, currently in clinical trials, and defibrotide, which is from a new drug class, the oligonucleotides. Defibrotide has been demonstrated to have remarkable activity in MM in-vivo models, enhancing and synergizing with other anti-MM drugs. This particular agent targets endothelial damage and microvascular injury in a way that may abrogate some important side effects we currently encounter, including deep vein and arteriolar thrombosis, and other microvascular toxicities.

H&O What challenges do these new therapies present?

PR With numerous options now available, how do we best deploy these options in the most rationale way to optimize patient outcome? For example, transplant has dominated MM treatment, and this modality is clearly very effective but can be toxic. How should transplant be integrated into the new treatment strategies? Patients could continue to receive up to 2 transplants, with small molecules being added, or it may be possible to reduce the number of transplants without decreasing efficacy and improve tolerability. Patients who have undergone numerous cycles of prior high-dose CT do not tolerate the new agents as well as patients who have received less CT, so we do need to figure out how the novel biologic therapies will fit into this evolving treatment landscape. Transplantation does provide a key platform. However, whether or not multiple transplants are needed is increasingly less clear in my opinion. As novel therapies are introduced into upfront treatment, patients are experiencing higher rates of complete responses and when they are used in maintenance, patients enjoy longer disease control, suggesting that new agents may not only be very useful in advanced-stage disease, but also completely change the way that MM is treated from diagnosis, through transplant and beyond.

Suggested Reading

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