Momentum in Multiple Myeloma Treatment

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Quintiles examines promising new approaches to more effective multiple myeloma treatments.

HIGH RESPONSE RATES INSPIRE HIGH HOPES

Multiple myeloma is considered to be incurable, with a treatment course characterized by remission followed by relapse, with each remission generally lasting a shorter duration than the last, and ultimately resulting in progressive disease and death. The expansion in classes of active agents and their use in combination has resulted in a significantly higher response rate, including complete response (CR’s) and partial response (PR’s) and correspondingly longer periods of remission.
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The last decade has seen an explosion in our understanding of myeloma and a proliferation of therapeutic options. We have gone from having little to offer using alkylating agents and steroids to a broad range of therapeutic options including cytotoxic agents, immunomodulatory agents, proteasome inhibitors, as well as cytoablateive therapy with hematopoietic stem cell transplantation (HSCT) in ever older patients. Developments in the myeloma field are reminiscent of the wide expansion of therapeutically active agents that was witnessed a decade earlier in breast cancer; essentially turning a uniformly lethal malignancy into a chronic disease. New agents continue to be developed for myeloma while exploring various combinations of existing agents to prolong the period of disease control in these patients.

Relying in part on information that is emerging about the genetic basis of the disease, investigators are pursuing a variety of strategies to control multiple myeloma approaches that kill tumor cells directly, inhibit the body’s production of substances that promote tumor cell growth and survival, inhibit the binding of tumor cells to bone marrow, or enhance the immune response against myeloma cells. Since July 2009, parts of the multiple myeloma genome have been identified and this insight may further improve the decisions for choosing the optimal therapy for the appropriate patient, and more reliably predict prognosis.

PROMISING EARLY RESULTS IN THREE NOVEL TREATMENTS
The treatment of multiple myeloma can be divided into three groups:

> Elderly patients and patients ineligible for transplant
> Younger and transplant-eligible patients
> Patients in the relapse/refractory setting

The aim of the treatment is remission prolongation, and ideally, to achieve complete remission.

Optimizing response rates in frontline therapy for patients who are HSCT candidates and those limited by age or co-morbidities is a primary goal in treatment planning and regimen choice. The management of multiple myeloma in the past decade has been dramatically altered by approval of three new agents: thalidomide, lenalidomide, and bortezomib. Mechanisms of actions of these agents are briefly described below.

Thalidomide was the first of newer agents introduced for myeloma treatment and revolutionized disease management. It is a potent immunomodulatory agent as well as having anti-angiogenic and anti-inflammatory activity. Additional agents in this class are lenalidomide and pomalidomide, both quite active in myeloma. Lenalidomide has a more favorable safety and efficacy profile while pomalidomide is showing promise in ongoing studies.

Velcade® (bortezomib) binds to the 26S proteasome. This proteasome regulates the production and function of important cellular proteins such as those governing apoptosis and also removes abnormal or misfolded proteins from the cell. Velcade inhibits the 26S proteasome, causing a build-up of abnormal proteins in the myeloma cells and their eventual death. Carfilozomib, a promising proteasome inhibitor that is in development, has a high level of selectivity for a single site on the proteasome as well as minimal cross-reactivity to other proteases. It also appears to have a longer duration of action than bortezomib. The proteasome pathway plays a central role in controlling intracellular turnover of proteins regulating cell growth and survival, stress responses, apoptosis and cell cycle and is a recognized target in myeloma treatment. Apoptosis of the myeloma cell is associated with proteasome inhibition.
Newer agents on the horizon which appear to hold some promise in myeloma include the mTOR inhibitor, temsirolimus, the monoclonal antibody elotuzumab, directed against CS1, a cell surface glycoprotein which is highly and uniformly expressed on myeloma cells, and vorinostat, a histone deacetylase inhibitor.

The myeloma therapy studies presented at the 51st ASH Annual Meeting were well attended and covered two broad areas — testing novel three (3) and four (4) drug combinations with the goal of demonstrating response rates, and more complete and durable complete responses. The second area of emphasis is on new therapies in early-stage testing, thereby expanding the potential anti-myeloma armamentarium. Below is a summary of presentations at the 51st ASH Annual Meeting.

INDUCTION AND MAINTENANCE TREATMENTS

In a multicenter randomized Phase III trial in 260 newly diagnosed multiple myeloma patients (>65 years), induction with bortezomib/melphalan/prednisone (VMP) followed by maintenance with bortezomib/thalidomide/lenalidomide (VT) showed better response compared to induction with bortezomib/thalidomide/prednisone (VTP) followed by maintenance with bortezomib/prednisone (VP). The progression free survival (PFS) was significantly longer in the (34 versus 23 months); weekly dosing of bortezomib decreased the risk of peripheral neuropathy. This combination of induction and maintenance therapy also appears to overcome the poor prognosis conferred by having high risk cytogenetics in elderly myeloma patients. (Mateos et al, Abstract No 3). Similar results were observed in another Phase III trial with maintenance with VT following induction with bortezomib/melphalan/prednisone/thalidomide (VMPT) (Palumbo et al, Abstract No 128). These studies highlight the importance of maintenance therapy in significantly prolonging PFS over that seen with induction only. Kumar et al, (Abstract No 127), reporting their phase II EVOLUTION study in previously untreated myeloma patients, noted a high overall response rate (ORR) of 94% to be marginally better in the 4 drug Velcade/dexamethasone/cyclophosphamide/Revlimid (VDCR) regimen compared to VDR and VDC. However, this came at the cost of more treatment-emergent adverse events (AE’s), including two possible treatment-related deaths from renal failure on the VDCR arm. It will be interesting to see the data again as the results mature.

COMBINATION TREATMENTS IN RELAPSE/REFRACTORY POPULATIONS

A phase I/II study of pomalidomide alone or in combination with dexamethasone in a heavily pre-treated population with relapsed/refractory disease showed an ORR of 38%, a duration of response (DOR) of 11.1 weeks, and a TTP of 8.3 weeks with pomalidomide alone (Richardson et al, Abstract No 301). The combination with dexamethasone showed an ORR of 38%, DOR of 14.2 weeks and TTP of 20 weeks, with several patients having stable disease on both groups. These are highly encouraging results warranting further exploration of pomalidomide in myeloma.

Combination treatment with bortezomib and the mTOR inhibitor, temsirolimus (Ghobrial et al, Abstract No 748) or of lenalidomide (Reece et al, Abstract No 132) provided clinical benefit. Although a short-term study, single treatment with carfilozomib was reported to be efficacious in patients with relapsed or refractory multiple myeloma with a median time to progression of 7.6 months (Wang et al, Abstract No 302). It was tested as a single agent in relapsed/refractory heavily pre-treated myeloma (including stem cell transplant, thalidomide, lenalidomide and anthracycline failures) showed 45% ORR and 63% clinical benefit rate (CBR). Vorinostat, in a small phase I study in combination with pegylated liposomal doxorubicin and bortezomib (Voorhees et al, Abstract No 306) in heavily pre-treated patients showed activity in 6 out of 7 evaluable patients, supporting a role for histone deacetylase inhibitors in this disease.

The science behind multiple myeloma:

Multiple myeloma, a malignancy of the plasma cells, shows increasing prevalence with age, with approximately 20,000 cases diagnosed annually in the US. The disease consists of the abnormal proliferation of plasma cells, a form of a white blood cell that is important in the immune system. These cells are derived by differentiation from lymphocytes and their normal role is in humoral immunity — to produce small protein molecules called antibodies that help the body defend itself against infections. Their abnormal clonal proliferation most often results in a collection of cells making the identical antibody. This is detected in the serum, upon electrophoresis and immunofixation, as a monoclonal band of protein. The monoclonal band is composed of an intact antibody directed against a single epitope. In addition, the cells may make an excess of the light chain component of the antibody and this can be detected in the serum as free circulating light chains or in the urine as Bence-Jones proteinuria. A small minority, often with more aggressive disease, have recognizable plasma cells but these either do not make any monoclonal antibody or, if they make it, are unable to secrete it, and hence do not have a detectable serum or urinary monoclonal paraprotein.
CONCLUSION
In general, proteasomal inhibitors and immunomodulatory agents, used in two-to-four drug combinations are efficacious in patients with multiple myeloma. The emerging data favors maintenance therapy following the more intensive induction phase. There are several promising new agents on the horizon which will enrich our therapeutic armamentarium and allow tailored and individualized therapies to optimize patient prognosis. Some limitations exist however, as most data with novel agents published to date are short-term. Based on the exciting preliminary data sets described herein, long-term study results are to be eagerly awaited.

REFERENCES
1. Mateos et al, Abstract No 3. Treatment with bortezomib/melphalan/prednisone (VMP) followed by maintenance with bortezomib/thalidomide (VT) showed longer progression free survival (PFS) compared to induction with bortezomib/talidomide/prednisone (VTP) followed by maintenance with bortezomib/prednisone (VP) in patients with multiple myeloma older than 65 years.


4. Richardson et al, Abstract No 301. A phase I/II multi-center, randomized, open label dose escalation study to determine the maximum tolerated dose, safety, and efficacy of pomalidomide alone or in combination with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide and bortezomib.

5. Ghobrial et al, Abstract No 748. Combination of weekly bortezomib and temsirolimus shows efficacy in relapsed or refractory multiple myeloma.

6. Reece et al, Abstract No 132. The combination lenalidomide/bortezomib/pegylated liposomal doxorubicin (PLD)/dexamethasone has shown efficacy in newly diagnosed multiple myeloma.


Dr. Dave oversaw a number of hematology and oncology studies at all phases of drug development, as well as providing drug development strategy and guidance. His areas of therapeutic experience include cancers of lung, breast, colorectal, brain, sarcoma, pancreas, prostate, melanoma and liquid tumors. He also leads the global therapeutic group for hematology and oncology.

Dr. Dave has fifteen years of academic hematology-oncology experience, during which he served as a P.I. on multiple studies. He also served as Chairman of an NIH Study Section and also chaired the Research and Development Committee at a major academic medical institution. In the latter capacity, Dr. Dave oversaw all research and IRB-related activity, reviewing and managing over 170 protocols annually.

He received his medical degree from the University of Sheffield Medical School, England and his residency training at Royal Medical Postgraduate Medical School System, University of London, England. He conducted basic research in gene regulation and gene therapy at the NIH. He is board certified in internal medicine, medical oncology and hematology and was previously Associate Professor of Medicine at George Washington University and Assistant Chief of Hematology and Chief of Laboratory of Molecular Hematology at the Veterans Affairs (VA) Medical Center in Washington, DC.

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Dr. Manderman is board certified in medical oncology and radiotherapy with ten years of practice experience at Karolinska University Hospital. He served as a sub-investigator for clinical trials in lung cancer, esophageal cancer, and head and neck tumors. He has four years experience in drug development as regional medical monitor for Wyeth CR&D - Nordic region, based in Solna, Sweden. Dr. Manderman monitored trials in phase I to IV mainly in Scandinavia, Russia and Baltic States. His areas of therapeutic expertise include breast cancer, renal cell carcinoma, non-Hodgkin lymphoma, chronic myelogenous leukemia, pediatric solid tumors and osteoporosis.

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