Management of Multiple Myeloma – A Look to the Future

Dr. A. Keith Stewart, MB.CHB., F.R.C.P.C.
Princess Margaret Hospital, Toronto, Canada
McLaughlin Centre for Molecular Medicine, University of Toronto

Multiple myeloma is a malignancy of the plasma cells in the bone marrow. Since the 1990s, the treatment of myeloma has advanced to the point that, although we still don't talk about a true cure, in some patients it has been turned into a chronic disease. Indeed, a growing number of patients are living ten or more years after diagnosis. We are also better at treating the complications of myeloma, such as bone thinning, fractures, anemia and infections.

The most common approach to multiple myeloma treatment is to use cytotoxic agents, such as the chemotherapy agent melphalan, or steroids such as prednisone or dexamethasone. Although these drugs are easy to give and are still fundamental to myeloma therapy, over time the disease may become less responsive to them. Consequently, new agents are needed, both for first line therapy and for the treatment of relapsed and/or refractory myeloma.

The good news is that within the past decade, research has given us a number of new, targeted treatment options. One of the first agents to emerge was thalidomide, a form of immunomodulatory drug (iMiD). Exactly how iMiDs work is still unclear, but by regulating the immune system they appear to have both anti-cancer and anti-inflammatory effects. REVLIMID® (lenalidomide) is a new and promising member of the iMiD class that has recently proven to be a powerful anti-myeloma drug.

PrVELCADE* (bortezomib) is another new agent that has recently been approved by Health Canada as an effective option for patients with myeloma who have relapsed following front-line therapy and are refractory to their most recent therapy. VELCADE* was the first type of cancer agent in the proteasome inhibitor category. In Canada, VELCADE* is currently approved for use as a single agent after other therapies have failed, but is showing evidence of effectiveness when combined with other therapies as an initial therapy or when used at the first disease relapse. Clinical trials of combination therapies are underway.

Other approaches that are in development include agents that interfere with different processes that contribute to myeloma, such as Vascular Endothelial Growth Factor (VEGF) or insulin-like growth factor inhibitors, histone deacetylase inhibitors, and heat shock protein inhibitors. Some of these new therapies target not only the myeloma cell, but also its bone marrow microenvironment.

One of the most exciting aspects of myeloma research is the insight we are making into the genetics of the disease. Using microchips we can study up to 30,000 genes in myeloma cells at the same time. This makes it possible to compare a gene sample from myeloma to those of normal cells, or cells representing different types of cancer. Using such tools we now know that myeloma is not one disease but has at least six different genetic sub-types. Three gene families have been identified that

define different myelomas. These genes make myeloma cells grow and thus are targets for treatment.

In a study of myeloma patients in Toronto, 15 percent of patients had myeloma that was dependent on one of these genes called Fibroblast Growth Factor Receptor 3. This abnormality was found to be linked to the IgA type of the disease and worse transplant outcomes. Patients with this gene tend to have a higher relapse rate, compared to those without this marker. Most excitingly, drugs which target this gene have just entered clinical trials for myeloma. In the future, the ability to identify the genetic sub-type will enable us to move into what can be called "risk adapted therapy" – tailoring the treatment to the specific genetic profile of each patient.

Knowing more about the genetics of myeloma will also open the door to understanding how current treatments such as VELCADE* or thalidomide work. For example, these drugs may "switch on" certain genes in myeloma cells that inactivate processes which contribute to the disease. These processes may help to explain why some patients respond well to certain therapies while others do not. Basic research is already underway on agents to "turn off" genes associated with myeloma or "turn on" processes that inhibit the disease. In the development of new knowledge and therapies, the involvement of patients is critical. Whenever possible, consider participating in clinical trials. You can also help by donating bone marrow samples for research.

For more information about treatments for multiple myeloma, check out the Web site of Myeloma Canada www.myelomacanada.ca, and the Web sites of the Multiple Myeloma Research Foundation (www.multiplemyeloma.org) or the International Myeloma Foundation (www.myeloma.org). Information for multiple myeloma is also available from your provincial cancer care agency.

Dr. Stewart is a Professor of Medicine at the University of Toronto. He obtained his medical degree at Aberdeen University Medical School and did specialized training in internal medicine and hematology at Queen's University, the University of Toronto and the New England Medical Center. Dr. Stewart also holds the J. Gerald Scott/David G. Whitmore Chair in Haematology and Gene Therapy Research, and is a leading researcher in hematology and blood cancers. He sits on numerous national and international committees and review panels, including the medical/scientific boards of the International Myeloma Foundation and the Multiple Myeloma Research Foundation. He has recently relocated to the Mayo Clinic (Scottsdale).

Supported by an unrestricted educational grant by Ortho Biotech and reflects the opinion of the author and not of the sponsoring company

VLNL052261E