Research Needs in Myeloma

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Myeloma is a complex disease in which we at present have no understanding of the proximal cause or initiating event, the molecular mechanisms responsible for disease progression from a dormant to active state, or cure. Many associations including chromosomal abnormalities and oncogene expression have been noted, but are neither universal nor apparently directly related to disease course or features. There is currently not an acceptable molecular or morphologic classification of the disease. Myeloma is associated with common and serious complications including skeletal involvement, renal failure, immune suppression and susceptibility to infection, which is often fatal. Chemotherapy regimens have improved prognosis only marginally over the past 30 years, and there is no currently recognized treatment which leads to cure. In these properties, myeloma suffers badly in comparison with the acute and chronic leukemias and lymphomas, in which in some cases there are recognized specific gene defects, understanding of the molecular mechanisms of the disease, molecular based classifications and treatment in some patients which is curative.

Some of the outstanding current needs in myeloma are:

1. Understanding the cause/initiating event.

The identification of critical oncogenes and tumor suppressor genes, the role of single gene polymorphisms, novel aberrations of the apoptotic machinery, and the part played by angiogenesis in the predisposition of patients to myeloma, are all fundamentally important issues. In each of the above, there are potential candidates currently being studied, but it appears likely that the critical players remain to be identified. Moreover, the causes of exacerbation/progression of the disease from MGUS to myeloma, and from plateau phase to active disease also require attention, in my view using not just patient studies but also appropriate animal models.

The role of the marrow microenvironment in myeloma has been shown to be critical to disease progression and identification of cell-cell interactions between myeloma cells and bone marrow stromal cells and other cells of the marrow. These cell-cell interactions require clarification, preferably using combinations of both in vitro and in vivo techniques.

2. Identification of novel therapies for the treatment of myeloma.

It is possible that current forms of chemotherapy may have little more to offer, and that bone marrow transplantation may also be close to its limit, unless there is a major technological advance that reduces mortality after allotransplantation. Thus, it is clear that novel new therapies are required.

These may come from better understanding of the molecular mechanisms responsible for disease initiation or exacerbation, or from understanding the key molecules responsible for myeloma cell survival. Techniques are now emerging for gaining insight into these events and identifying these molecules. For example, cell-cell interactions are likely essential for myeloma cell survival. Interrupting these interactions by antagonists or antibodies would likely be an effective method for treatment of the disease.

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3. Understanding the pathophysiology of the complications of myeloma, and identifying better treatments for these complications.

Myeloma is complicated in many patients by infection, renal failure and skeletal involvement. Infection occurring during the first few months of treatment is a bad prognostic sign, and requires further attention. Renal failure is a major problem, and better understanding of the pathophysiology may be helpful in preventing this from occurring. The skeletal complications remain a difficult problem, still not adequately understood, and more attention is required to identify even better treatments than the bisphosphonates.

There are a number of obstacles to research in myeloma that have retarded progress. The first is that it is a relatively uncommon disease. The fact that myeloma is uncommon lessens interest of the pharmaceutical companies in this disease because the markets are limited, and lowers the interest of major funding bodies relative to more prominent diseases such as breast cancer or prostate cancer. Advocacy of the need for more research in myeloma by groups such as the nonprofit International Myeloma Foundation, by researchers and by influential patients might improve this situation. Secondly, until recently there has been a lack of good animal models. Most researchers study myeloma using clonal cell lines or by clinical studies in patients. Data from the cell lines may be misinterpreted for a number of reasons, the most important of which may be that myeloma cells in vivo interact closely with other cells in their microenvironment that influence their behavior. Studies on patients with myeloma are very difficult because it is a complex disease with multiple complications, and with many variables which confound interpretations that can be made from single interventions. Valid and reliable animal models of the disease are required for a) identification and validation of pathophysiologic mechanisms; b) preclinical testing of novel new treatments; c) investigation of the pathophysiology and treatment of disease complications; d) identification of specific genes and possibly viruses related to the disease; e) identification of molecular mechanisms responsible for transformation of MGUS to myeloma.

Although there is currently no cure for myeloma, there are entirely new approaches to treatment which offer the hope for better future care. Despite all of these obstacles, new agents such as thalidomide, proteasomal inhibitors, arsenic trioxide, and inhibitors of RANK signaling all show marked promise in either clinical studies or in animal models. There is now sufficient interest in this disease that the future looks promising for far more effective therapies than those currently available.