Multiple myeloma

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DIAGNOSIS AND FOLLOW-UP OF MONOCLONAL GAMMOPATHIES

It is extremely important to distinguish between myeloma and monoclonal gammopathy of undertermined significance (MGUS) or smoldering myeloma. The basic absence of symptom or other lab features indicative of a progressive plasma cell process. A number of techniques are now available to help in the evaluation of such patients. The plasma cell labeling index in the bone marrow or peripheral blood is particularly helpful. A "0" labeling index indicates MGUS whereas a higher value is more compatible with active disease. Various scanning techniques are helpful to evaluate the extent of involvement of the bones and or bone marrow. Screening MRI, whole body MIBI scanning, and PET scanning are particularly useful for the detection of active disease and also to show the pattern of the disease throughout the skeleton. In addition bone density testing can be helpful to evaluate borderline osteopenia and assess if early bone disease is evolving. The evaluation of early bone disease is particularly important because of the availability of bisphosphonate therapy. Other testing which can help distinguish between myeloma and smoldering myeloma includes cytogenetic molecular analysis, and also the assessment of the cytokine production by the bone marrow plasma cells. Of interest chromosome abnormalities have been detected using the FISH technique even in patients with MGUS. Conversely, production of ILB1β is a characteristic feature of patients with active myeloma with bone destruction. Detailed immuno phenotypic analysis of the plasma cells can also be helpful to determine the likelihood of myeloma vs more indolent disease. Occasionally even with extensive testing it may be impossible to be certain if active disease is imminent and the only procedure available will be to monitor that patient with careful evaluation of blood, urine and other testing. With the availability of new technologies particularly the potential of idiotypic vaccine and anti viral approaches it may be that early intervention may be helpful and important to patients with slowly evolving multiple myeloma.

PATHOGENESIS AND MOLECULAR BIOLOGY OF MYELOMA

Myeloma results from a combination of genetic and acquired factors. The genetic factors are as yet not fully understood, but include polymorphisms in the P450 and GST genes as well as immune regulatory defect most likely involving auto antigen recognition and/or regulation of retro-virus activation. Myeloma is more common in men and blacks and the incidence increases with age. Exposure to toxic chemicals, particularly petro chemicals, including agent orange and pesticides as well as radiation exposure are linked to the development of myeloma. Specific trigger factors have been implicated including both viral and bacterial infections. The genetic factors, toxic exposure plus infective trigger factors will be better delineated with time. This raises the possibility of both counseling and preventive strategies.

No single genetic abnormality is uniformly associated with multiple myeloma although abnormalities involving the 14q32 break point are the most frequent. At the molecular level several abnormalities of

oncogenes and tumor suppressors have been noted including abnormalities of P53, Rb, and Bcl-2 appears that progressive mutation occurs as myeloma evolves to produce numerous abnormalities at the chromosome level as well as multiple molecular defects. These result in multiple abnormalities in the cytokine loop systems. Most characteristic of myeloma is the increased production of IL6 as well as IL1β, both of which contribute to the development of bone disease. Recent studies also implicate metalloproteinases (MMP) which produce destruction of bone matrix. There are therefore numerous targets for therapeutic intervention both at the molecular and cytokine level. Although the stem cell origin of myeloma remains some what controversial the majority of studies confirm that myeloma is a disease of the plasma cell which has undergone immunoglobulin chain rearrangement and affinity maturation. The myeloma cell is therefore still the logical target for new treatment strategies.

TREATMENT UPDATE IN MYELOMA

The basic treatment outcome for myeloma has not changed remarkably over the past 20 years. However in the past 10 years high dose therapy has been introduced. High dose melphalan with peripheral stem cell rescue is available for consolidation of responding patients following initial induction as well as for patients with relapsing disease. Although greater cell kill is clearly possible, the full impact upon remission duration and overall survival is not so clear cut. There are patients with good risk prognostic factors such as low bet 2 and low labeling index. The overall impact of high dose therapy would seem to be great. However, for patients with more aggressive disease manifest by high beta 2 microglobulin and high labeling index better and longer remissions can be achieved and overall survival would seem to be improved. Unfortunately high dose therapy utilizing allogenic or twin transplant for support is nor curative. Twin transplant is clearly an option for those patient lucky enough to have an identical match. Allogeneic transplant remains a highly risky procedure.

Perhaps the most encouraging areas of new treatment are in the area of supportive therapy. This may represent a new form of therapy that can have a significant impact in reducing bone complications. For example pamidronate 90 mg over 4 hours once a month can reduce the likelihood of bone complications by 50%. Newer bisphosphonates might be of additional benefit. Other important aspects for supportive care include the use of IV gamma globulins, GCSF, and erythropoietin. Promising new strategies include metalloproteinase and vitamin D^3 inhibitors. As far as new chemotherapeutic agents a group of drugs capable of reversing multi drug resistance are important particularly PSC833 which is currently undergoing clinical trial. Approximately 30% of patients with VAD resistance disease can have further response with VAD plus PSC833. Another area of interest is the substitution of Adriamycin with idaru-bicin and oral anthracycline. It seems that a complete oral combination of idarubicin plus dexamethasone can be used instead of the IV VAD regimen. Other areas of interest include the development of anti idiotypic strategies with patients in remission following initial induction therapy. There are therefore many promising new strategies.