Venue: PYRAMID 1
21st August 2007
1130-1245 hr

Symposium 1B: New Developments in myeloma management

S1B-1. Pathogenesis of myeloma – insights from dtZ trial

Teoh G

Department of Haematology, Singapore General Hospital, Singapore

Multiple myeloma (MM) cells require substantial support from the tumor bed for both survival and growth. In fact, direct interaction between MM cells and cells of the bone marrow (BM) microenvironment (especially osteoclasts) is necessary for the development of MM. Prior studies in severe combined immunodeficiency mice implanted with human bone, BM and MM cells have demonstrated that removal of osteoclasts not only eradicates MM, but also prevents its development. Accordingly, we tested the clinical anti-tumor effect of the highly potent anti-osteoclastic drug, zoledronic acid (ZOMETA) against a backdrop of low-dose dexamethasone (Dex)/thalidomide (Thal) in patients with various stages of MM; i.e. "dtZ". Importantly, ZOMETA was administered at a higher (3-weekly) than conventional (4-weekly) frequency in these studies. The superiority of "dtZ" over other regimens can be seen in the table below:

MM Status	Regimen	Response Rate	Complete Remission or Near Complete Remission	Chi Square p Value
New Cases	"dtZ"	100%	45%	-
	Thal/Dex	70%	20%	<0.001
	VAD	55%	10%	<0.001
Relapsed/Refractory	"dtZ"	62%	8%	-
	VELCADE	25%	3%	<0.001
	Dex	5%	0%	<0.001

Since osteoclasts are derived from peripheral blood monocytes, and a significant correlation between the absolute monocyte count (AMCO) and stage of MM exists, we postulate that a "monocyte loop" could possess the capacity to drive osteoclast renewal and MM cell survival and growth. Accordingly, data from the "dtZ" studies demonstrate that patients treated with higher-frequency (but not conventional doses of) ZOMETA express decreased AMCO levels, suggesting that ZOMETA at high dose rates could block the "monocyte loop". We therefore conclude that the "dtZ" regimen is highly effective because it specifically inhibits a critical tumorigenic process in MM, i.e. the "monocyte loop"; and this is possible only when ZOMETA is administered at a sufficiently high dose rate.

S1B-2. New and relevant investigations for diagnosis and monitoring in myeloma

Gibson J

Institute of Haematology, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia

Internationally recognised criteria have been established for the diagnosis, prognosis assessment and response assessment in patients with myeloma. In addition to clinical parameters, a limited number of

well-established laboratory tests are required to accurately define myeloma patients. This minimum laboratory set includes a full blood count, biochemical screen, serum and urine paraprotein (or light chain) identification, characterisation (by immunofixation) and quantitation, bone marrow aspirate (or tissue biopsy) and a serum beta-2 microglobulin. The myeloma literature is however "littered" with reports of a large number of other (potentially) useful investigations. Some of the more "well established" of these assays include bone marrow plasma cell morphology, flow cytometric analysis of plasma cells, cytogenetics and "immunological assays". To these we can now add the free light chain assay, flourescent in situ hybridisation (FISH), molecular profiling and assays to assess bone metabolism.

The potential application of these "newer" investigations is currently under intensive investigation. For instance, the use of conventional cytogenetics in many patients has previously been was severely limited by the low mitotic index and the presence of multiple complex abnormalities of the myeloma cells. FISH analysis has however revolutionised our understanding of the genetic lesions in myeloma such that this assay is now considered to one of the most powerful prognostic indicators. By extrapolation, molecular (gene) profiling may, in the future, provide even more useful prognostic data. Similarly, the recognition of osteonecrosis of the jaw (ONJ) and its relationship to therapeutic use of bisphosphonates has spurred an increase in interest in markers of bone metabolism. With such assays it is hoped that we can more accurately identify of those patients who would most benefit from this class of agents, when such agents can be stopped and aid in the development of alternative therapies.

S1B-3. Are newer agents for myeloma treatment curative?

Ng SC

Consultant Haematologist, Subang Jaya Medical Centre, Petaling Jaya, Selangor, Malaysia

Multiple myeloma (MM) is a B cell malignancy characterized by the accumulation of terminally differentiated clonal plasma cells in the bone marrow, the production of monoclonal immunoglobulin detectable in the serum and/or urine, and presence of lytic bone lesions. Without treatment, new symptomatic cases rarely survive beyond a year. Conventional chemotherapy regimens such as mephalan/prednisolone and the more intensive regimens e.g VAD (vincristine,Adriamycin,Dexametha sone) extends the median survival to 30 months. However, the complete remission (CR) rate remained a low 10-15%.The advent of **autologous bone marrow transplant** raised the CR rate to 30-50% and extend the overall survival to 60 months.

Thalidomide is a significant breakthrough in treatment as it is highly effective and achieved a CR rate of 14% even in refractory cases**.** Being an anti-angiogenesis agent it is capable of altering the BM microenvironment and can directly inhibit the growth and survival of myeloma cells. **Bortezomib** (velcade) was the next star novel agent and it is a proteosome inhibitor. By blocking the NF-KB pathway, the myeloma cells undergo apoptosis .The use of **bisphosphonates** is effective in reducing the skeletal events in myeloma. Newer novel agent such as **lenalidomide (**thalidomide analogue) has been shown to be more potent with less potential side effects. More targeted drugs are in the horizon as the biology and pathogenesis of the disease is better understood. **Heat shock protein (Hsp) inhibitor** has shown promising results in early studies. The availability of potent anti-myeloma agents opens the doors for effective combination therapy. Meanwhile the transplant physicians are making progress in reducing the high transplant related mortality in allogenic transplant with the use of non myeloablative regimen.

With rare exceptions, the current treatment strategies **do not cure** MM. However, the ever improving results achieved with new agents in terms of higher CR and longer overall survival raises hope that cure for MM is an attainable goal in the near future.