biomnis
SPECIALISED MEDICAL PATHOLOGY
Focus
issue 24

A cytogenetic approach to plasma cell proliferation in Multiple Myeloma

Notes

Multiple Myeloma (MM) is the 2nd most frequent haematological malignancy in France and represents approximately 2 % of the mortality rate due to cancer. The mean age of onset is between 60 – 70 years. Multiple Myeloma remains an incurable disease. The clinical diagnosis of MM relies on three factors: the presence of a monoclonal immunoglobulin, the presence of plasma cells in the bone marrow and clinical visceral manifestations (CRAB: hypercalcemia, renal failure, anaemia and bone lesions). The initial clinical profile must:
Confirm the diagnosis, assess the prognosis, and indicate the parameters that will allow us to assess the treatment response. The Durie-Salmon staging system (1975) and the ISS (International Staging System – 2005) are currently the 2 classification systems known to assess the prognosis of Multiple Myeloma. The Durie-Salmon Staging System is based on the haemoglobin concentration, calcium concentration, immunoglobulin type and radiography data. ISS is based on the quantification of serum β2 micro globulin and albumin.
Recently a new significant prognostic factor has been revealed: cytogenetic analysis of tumour plasma cells. Symptomatic multiple myeloma cytoreductive treatment relies (together with the stage of the disease and the age of the patient) on the combination of chemotherapies and BMT.

Cytogenetics and Multiple Myeloma

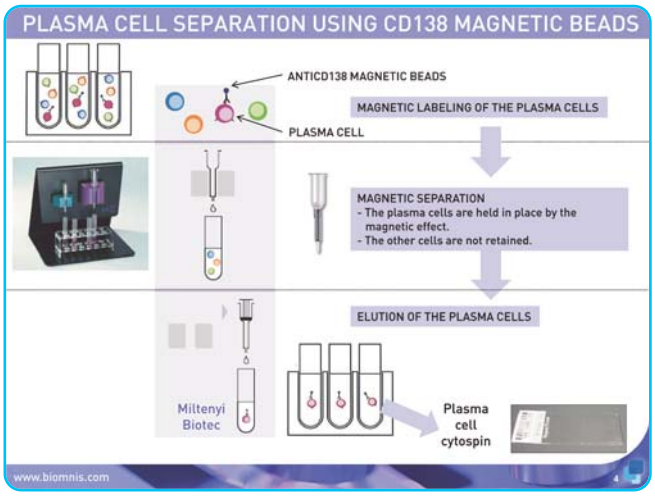
Cytogenetic analysis for MM has two objectives: to assess the prognosis and to adapt the future treatments.

Technical difficulties in cytogenetic analysis for MM

MM cytogenetic analysis is technically difficult for 2 reasons. Firstly, there is often a 'dilution' of the tumour plasma cells in the bone marrow samples due to aggregation of the tumour plasma cells by cell colony (heterogenicity of plasma cell clusters) and there is often partial bone marrow plasma cell infiltration. This phenomenon causes variability in the infiltration percentage. Secondly, the tumour plasma cells show a low mitotic index and the mitogenic agents used are almost always efficient. These two reasons explain why cytogenetic factors took so long to be used as major prognostic factors for Multiple Myeloma.

The purification of tumour plasma cells for cytogenetic analysis is essential.

The purification of bone marrow samples is essential. Selective separation on CD138 magnetic beads enriches the interphasic preparations before FISH (Fluorescent in Situ Hybridisation) is used to obtain a prognosis. The selected fluorescent probes allow us to evaluate the anomalies with prognostic value. A karyotype is also performed in order to elaborate the results obtained via the interphasic FISH technique.



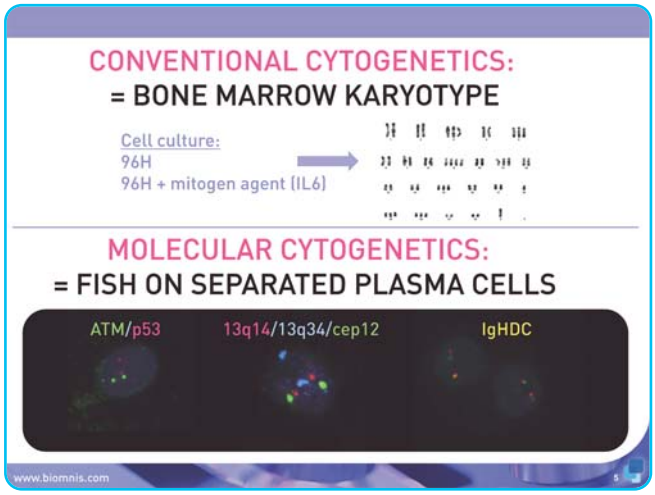
Chromosomal anomalies associated with MM

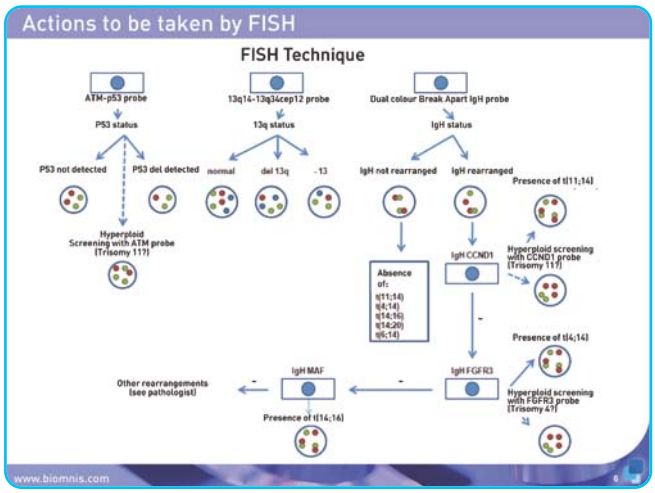
The main cytogenetic anomalies described in MM are either numerical or structural abnormalities.

Numerical abnormalities are schematically separated into two groups: 1) Hyperdiploidy 2) Hypodiploidy, pseudodiploidy and near-tetraploidy. The modal chromosome number for a Hyperdiploidy abnormality is approximately 53 chromosomes, with a gain in chromosomes 3, 5, 7, 9, 11, 15, 19 and 21.
Hyperdiploidy abnormalities represent approximately 50 % of cases. Chromosomal losses encountered in hypoploidy abnormalities concern the chromosomes 13, 14, 16 and 22. Near-tetraploidy abnormalities could be derived from hypodiploidy or pseudodiploidy cellular clones.

Structural abnormalities implied in MM principally involve the loci IgH (14q32), p53 (17p13), thechromosome 13 or chromosome 1 (gain of 1q).

14q32 (IgH) band rearrangements are identified in 55 - 70 % of cases. The translocations described are: t(11;14)(q13;q32) in 15 - 20 % of cases, t(4;14)(p16;q32) in approximately 15 % of cases or the translocations t(14;16)(q32;q23), t(14;20)(q32;q11) or t(6;14)(p21 ;q32) in less than 5 % of cases respectively. In 20 % of cases the IgH partner is not identified. In 40 – 50 % of cases, monosomy 13 is observed or, on rarer occasions the deletion del(13q). There is also a frequent association between the translocations t(4;14) or t(14;16) and the loss of a chromosome 13. Finally, the deletion del(17p) has been identified in less than 10 % of cases.

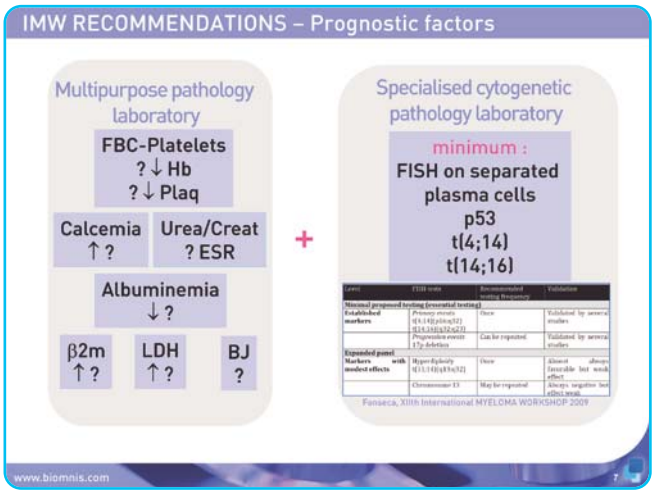


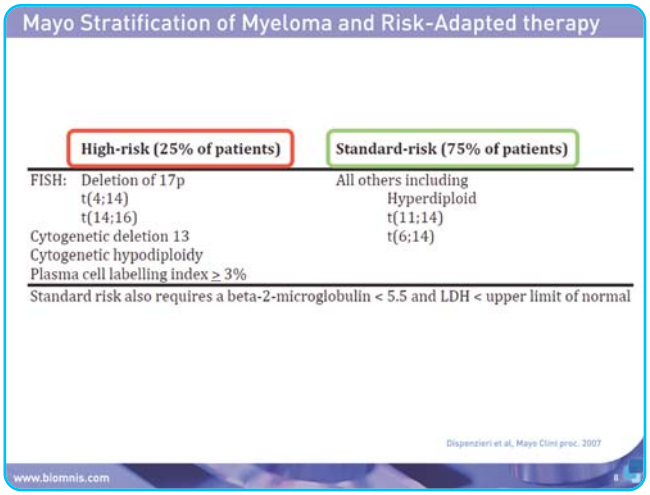


Cytogenetic abnormalities described in MM that show high prognostic value

The previously described chromosome abnormalities showing high prognostic value in MM were: the 'hyperdiploidy' Myeloma is associated with a favourable prognosis whereas myeloma showing del(17p), t(4;14) or t(14;16) are associated with a poor prognosis.

The prognostic stratification put forward by the Mayo clinic is based on criteria seen in the following diagram.





From routine cytogenetics to pangenomic molecular genetics and molecular biology

Innovative pangenomic molecular cytogenetic techniques (CGH array) and molecular biology techniques (SNP array and expression chips) seem to be able to identify the prognostic groups better than the current classifications used as well as cytogenetic investigations.

Conclusion and perspectives

The clinical aspects of the Durie-Salmon and ISS classification systems are still used today for the prognostic stratification of MM patients. The genetic data allows us to perform a molecular classification of this malignant blood disease and to propose good prognostic factors and therapy.

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