Research Article

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Multiple Myeloma's Molecular Cytogenetics.

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ABSTRACT

A plasma cell malignancy known as multiple myeloma (MM) is typified by several genetic abnormalities. It is possible to discriminate between two primary categories of abnormalities: hyperdiploid and hipodoploid, where the chromosome number is primarily composed of either by monosomies or trisomies, in turn. The development of Fluorescence In Situ Hybridization (FISH) has made it possible to detect genomic abnormalities that are included in prognostic scoring systems that also account for clinical factors. This straightforward analysis can inform the patient's initial assessment and help tailor his care.

Keywords : Myeloma; Cytogenetics; Fish

INTRODUCTION

Unlike acute leukemias, Multiple Myeloma (MM) is characterized by chromosomal abnormalities that can be investigated using conventional methods.

Low mitotic activity of tumor cells has impeded cytogenetics in this disease [1,2]. The use of molecular-based cytogenetic tools in analyzing MM and its predecessor, Monoclonal Gammopathy of Undetermined Significance (MGUS), has led to significant improvements in understanding plasma cell tumor biology. Fluorescence In Situ Hybridization (FISH) can reveal complex chromosomal abnormalities in almost all MM and MGUS patients, providing valuable prognostic information [3].

Conventional cytogenetics

Cytogenetic analysis is only useful for less than 30% of MM patients due to the high mitotic activity of tumor cells in MM, which is higher than in other haematological illnesses. low. Nearly half of individuals have a complicated karyotype with over 10 anomalies [4].

Numerical changes

The numerical changes include monosomies on chromosomes 13, 14, 16, and 22, and trisomies on chromosomes 3, 5, 7, 9, 11, 15, 19, and 21 [5]. Regardless of the finding of specific Chromosome banding analysis can provide significant prognostic information by detecting aberrant metaphases and tumor cell ploidy in informative cases [6]. Patients with a normal karyotype have a much longer life rate than those with cytogenetically abnormalities [7]. Tumors with abnormal metaphases can be classified based on their chromosomal number, which might impact prognosis. Hypodiploidy has been linked to poorer outcomes across multiple studies. However, undesirable genetic characteristics, such as monosomy 13/13q deletion and t(4;14).

The numerical changes include monosomies on chromosomes 13, 14, 16, and 22, as well as trisomies on chromosomes 3, 5, 7, 9, 11, 15, 19, and 21 [5]. Regardless of the identification of specific Chromosome banding analysis can provide important prognostic information by detecting abnormal metaphases and tumor cell ploidy in relevant circumstances [6]. Patients with a normal karyotype live a significantly longer life than those with cytogenetically abnormalities [7]. Tumors with aberrant metaphases can be classified according to their chromosomal number, which may affect prognosis. Hypodiploidy has been associated to inferior outcomes in numerous studies. However, unfavorable genetic traits, such as monosomy 13/13q deletion and t(4;14), In MM, test for 13q14 and 17p deletions (13q-, 17p-), IGH locus translocations (t(4;14)(p16.3;q32), t(11;14)(q13;q32), t(14;16)(q32;q23), and abnormalities of the chromosomes 1p and 1q [2]. The majority of these probes are available.

Most laboratories use probes to detect 13q deletion in chromosomal band 13q14, although the essential area of 13q- remains unclear. Probes that contain the p53 gene are commonly used to detect 17p-. DNA probes can identify translocations in the immunoglobulin heavy-chain (IgH) locus by mapping to both the constant (CH) and variable regions [13]. Differentially labeled probes colocalize to detect reciprocal translocations.

Colocalization of differently labeled probes for IgH and its translocation partner (e.g. 11q13, 4p16, 16q23), ideally on both derived chromosomes (double fusion). The cut-off levels for positive results are based on bone marrow samples from healthy participants. For dual fusion or break-apart probes, a

10% cut-off level is acceptable. For single fusion results with dual fusion probes, a 20% cut-off level is recommended. However, some laboratories use a 10% threshold. Proper cut-off levels should be chosen by each laboratory [2].

13q deletion

FISH investigations indicate that -13/13q- is present in approximately 50% of MM patients, making it the most common aberration [14]. Using standard cytogenetics, the incidence of chromosomal 13 deletions Patients with informative karyotypes have a comparable incidence of 10% to 20%, as established in major cytogenetic studies.

series. In patients with t(4;14)(p16.3;q32) or t(14;16)(q32;q23), roughly 90% have -13/13q-. In traditional cytogenetics, -13/13q- is linked to a poorer response rate.

MM is associated with higher rates, shorter event-free survival (EFS), and lower overall survival (OS). This applies to individuals who have undergone conventional chemotherapy, High-Dose Chemotherapy (HD-CTX), or Autologous Stem Cell Transplantation (ASCT) [15].

Karyotyping for -13/13q- results in a worse prognosis than FISH for the identical anomaly. This finding is likely owing to a combination of poor prognostic indicators, including a greater rate of proliferating cells [16]. FISH identifies considerably more 13q-deleted patients than conventional cytogenetics (40-50% versus 15-20%).

17p deletion

Mutations or deletions of the p53 tumor suppressor gene have been linked to disease development in many human cancers. In most FISH datasets, the occurrence of p53 Deletion rates among newly diagnosed individuals were between 5% and 10% [17,18]. Functional deletion of the gene is seen in up to 40% of advanced myeloma patients and over 60% of human myeloma cell lines, indicating tumor progression [19]. FISH-identified deletion of the p53 gene region predicts poorer survival rates regardless of treatment method (conventional or HD-CTX) [20].

Chromosome 1q

Cytogenetic studies have linked 1q aberrations to advanced illness, tumor development, and shorter event-free survival. The gene implicated appears amplified and is CKS1B, a cell cycle regulator located on chromosomal band 1q21, has been linked to a poor prognosis [21-23].

CONCLUSION

Using cytogenetics and molecular cytogenetics to analyze genomic rearrangements in MGUS and MM has helped us better comprehend clonal plasma cell diseases. Evaluation of a complete panel of chromosomal imbalances and translocations is essential for clinical care.

REFERENCES

1. Fonseca R, San Miguel J. Prognostic factors and staging in multiple myeloma. Hematol Oncol Clin North Am. 2007; 21: 1115-1140.
2. Ross FM, Avet-Loiseau H, Ameye G, Gutiérrez NC, Liebisch P, O'Connor S, et al. Report from the European Myeloma Network on interphase FISH in multiple myeloma and related disorders. Haematologica. 2012; 97: 1272-1277.
3. Gozzetti A, Le Beau MM. Fluorescence in situ hybridization: uses and limitations. Semin Hematol. 2000; 37: 320-333.
4. Sawyer JR. The prognostic significance of cytogenetics and molecular profiling in multiple myeloma. Cancer Genet. 2011; 204: 3-12.
5. Avet-Loiseau H. Role of genetics in prognostication in myeloma. Best Pract Res Clin Haematol. 2007; 20: 625-635.
6. Fonseca R, Barlogie B, Bataille R, Bastard C, Bergsagel PL, Chesi M, et al. Genetics and cytogenetics of multiple myeloma: a workshop report. Cancer Res. 2004; 64: 1546-1558.
7. Barlogie B, Shaughnessy JD. Early results of total therapy II in multiple myeloma: implications of cytogenetics and FISH. Int J Hematol. 2002; 76: 337-339.
8. Higgins MJ, Fonseca R. Genetics of multiple myeloma. Best Pract Res Clin Haematol. 2005; 18: 525-536.
9. Cigudosa JC, Calasanz MJ, Odero MD, Prosper F, Etxaniz A, Marin J, et al. Cytogenetic data in 41 patients with multiple myeloma. Karyotype and other clinical parameters. Cancer Genet Cytogenet. 1994; 78: 210-213.
10. Dewald GW, Therneau T, Larson D, Lee YK, Fink S, Smoley S, et al. Relationship of patient survival and chromosome anomalies detected in metaphase and/or interphase cells at diagnosis of myeloma. Blood. 2005; 106: 3553-3558.
11. Avet-Loiseau H, Durie BG, Cavo M, Attal M, Gutierrez N, Haessler J, et al. Combining fluorescent in situ hybridization data with ISS staging improves risk assessment in myeloma: an International Myeloma Working Group collaborative project. Leukemia. 2013; 27: 711-717.
12. Hose D, Seckinger A, Jauch A, Rème T, Moreaux J, Bertsch U, et al. The role of fluorescence in situ hybridization and

gene expression profiling in myeloma risk stratification. Srp Arh Celok Lek. 2011; 139: 84-89.

13. Bergsagel PL, Kuehl WM. Chromosome translocations in multiple myeloma. Oncogene. 2001; 20: 5611-5622.
14. Avet-Louseau H, Daviet A, Sauner S, Bataille R. Intergroupe Francophone du Myélome. Chromosome 13 abnormalities in multiple myeloma are mostly monosomy 13. Br J Haematol. 2000; 111: 1116-1117.
15. Becze E. Cytogenetics helps determine diagnosis and prognosis for multiple myeloma. ONS Connect. 2012; 27: 18-19.
16. Chiecchio L, Protheroe RK, Ibrahim AH, Cheung KL, Rudduck C, Dagrada GP, et al. Deletion of chromosome 13 detected by conventional cytogenetics is a critical prognostic factor in myeloma. Leukemia. 2006; 20: 1610-1617.
17. Avet-Loiseau H, Li JY, Godon C, Morineau N, Daviet A, Harousseau JL, et al. P53 deletion is not a frequent event in multiple myeloma. Br J Haematol. 1999; 106: 717-719.
18. Chng WJ, Price-Troska T, Gonzalez-Paz N, Van Wier S, Jacobus S, Blood E, et al. Clinical significance of TP53 mutation in myeloma. Leukemia. 2007; 21: 582-584.
19. Lodé L, Eveillard M, Trichet V, Soussi T, Wuillème S, Richebourg S, et al. Mutations in TP53 are exclusively associated with del(17p) in multiple myeloma. Haematologica. 2010; 95: 1973-1976.
20. López-Anglada L, Gutiérrez NC, García JL, Mateos MV, Flores T, San Miguel JF. P53 deletion may drive the clinical evolution and treatment response in multiple myeloma. Eur J Haematol. 2010; 84: 359-361.
21. Avet-Loiseau H, Attal M, Campion L, Caillot D, Hulin C, Marit G, et al. Longterm analysis of the IFM 99 trials for myeloma: cytogenetic abnormalities [t(4;14), del(17p), 1q gains] play a major role in defining long-term survival. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2012; 30:1949-1952.
22. Chang H, Qi X, Trieu Y, Xu W, Reader JC, Ning Y, et al. Multiple myeloma patients with CKS1B gene amplification have a shorter progression-free survival post-autologous stem cell transplantation. Br J Haematol. 2006; 135: 486-491
23. Marzin Y, Jamet D, Douet-Guilbert N, Morel F, Le Bris MJ, Morice P, et al. Chromosome 1 abnormalities in multiple myeloma. Anticancer Res. 2006; 26: 953-959.
24. Fonseca R, Debes-Marun CS, Picken EB, Dewald GW, Bryant SC, Winkler JM, et al. The recurrent IgH translocations are highly associated with nonhyperdiploid variant multiple myeloma. Blood. 2003; 102: 2562-2567.
25. Avet-Loiseau H, Facon T, Daviet A, Godon C, Rapp MJ, Harousseau JL, et al. 14q32 translocations and monosomy 13 observed in monoclonal gammopathy of undetermined significance delineate a multistep process for the oncogenesis of multiple myeloma. Intergroupe Francophone du Myelome. Cancer research. 1999; 59: 4546-4550.
26. An G, Xu Y, Shi L, Zou D, Deng S, Sui W, et al. t(11;14) multiple myeloma: a subtype associated with distinct immunological features, immunophenotypic characteristics but divergent outcome. Leukemia research. 2013; 37: 1251-1257.
27. Avet-Loiseau H, Garand R, Lodé L, Harousseau JL, Bataille R. Intergroupe Francophone du Myélome . Translocation t(11;14)(q13;q32) is the hallmark of IgM, IgE, and nonsecretory multiple myeloma variants. Blood. 2003; 101: 1570-1571.
28. Fonseca R, Blood EA, Oken MM, Kyle RA, Dewald GW, Bailey RJ, et al. Myeloma and the t(11;14)(q13;q32); evidence for a biologically defined unique subset of patients. Blood. 2002; 99: 3735-3741.
29. Avet-Loiseau H, Brigaudeau C, Morineau N, Talmant P, Lai JL, Daviet A, et al. High incidence of cryptic translocations involving the Ig heavy chain gene in multiple myeloma, as shown by fluorescence in situ hybridization. Genes, chromosomes & cancer. 1999; 24: 9-15.
30. Chang H, Sloan S, Li D, Zhuang L, Yi QL, Chen CI, et al. The t(4;14) is associated with poor prognosis in myeloma patients undergoing autologous stem cell transplant. Br J Haematol. 2004; 125: 64-68.
31. Winkler JM, Greipp P, Fonseca R. t(4;14)(p16.3;q32) is strongly associated with a shorter survival in myeloma patients. Br J Haematol. 2003; 120: 170-171.
32. Avet-Loiseau H, Malard F, Campion L, Magrangeas F, Sebban C, Lioure B, et al. Translocation t(14;16) and multiple myeloma: is it really an independent prognostic factor? Blood. 2011; 117: 2009-2011.
33. Rajkumar SV. Multiple myeloma: 2013 update on diagnosis, risk-stratification, and management. Am J Hematol. 2013; 88: 226-235.