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Hyperdiploid multiple myeloma-cytogenetic and clinical aspects

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Abstract

In the current research the attention is focused on the possibilities of identifying a hyperdiploidy myeloma clone (HdMC) by using a triple-color fluorescence "in situ" hybridization (FISH) probe. The cytogenetic results from the bone marrow aspirates of 26 patients with newly diagnosed multiple myeloma admitted in the Hematology Department of our hospital during the period from March to September 2023 have been analyzed. The group consists of 12 female and 14 male patients with an average age of 67 years. A FISH probe for establishing hyperdiploidy myeloma clone was used as well as the most common methods for detecting genetic aberrations affecting the long and short arms of the 1 and 14q32 chromosome rearrangements. According to the results, two subgroups of patients have been established. The first subgroup consists of the patients with positive FISH probes for hyperdiploidy myeloma and/or 14q34 rearrangements and 1q25/1p36, while the second one consists of patients, negative for all the three probes listed above. A comparison between the demographic, laboratory data and the ISS (International Staging System) stage of the two subgroups has been made. The collected data suggests that the use of the triple-color FISH probe, as well as some other factors in the analyzed information, increases the probability of detecting a HdMC by 23%.

Keywords: Multiple myeloma; Hyperdiploidy clone; FISH; Triple-color probe

1. Introduction

Multiple myeloma (MM) is a hematological disease characterized by proliferation of the plasma cells in the bone marrow and is extremely heterogeneous regarding the clinical picture and the genetic aberrations. MM comprises 1.8% of all the malignant diseases in the USA, 18 % of the hematological malignancies and 2% of all the deaths caused by cancer [1]. The identification of genetic alterations is proven to be important for staging, for choosing a therapeutic approach and the survival of the patients. The primary genetic abnormalities in MM are: 14q32 rearrangements, deletion of the short arm of the chromosome 1 in the 1p36 region, amplification of the long arm of the chromosome 1 1q21 and 1q25 and trisomy of the odd chromosomes – 3, 5, 7, 9, 11 and 15. Deletion of the long arm of the chromosome 13 and deletion of the short arm of the chromosome 17 affecting the tumor suppressor gene TP53 are mainly secondary aberrations related to a poor prognosis [2]. The conventional cytogenetic methods and the use of the G-bending technic are very limited due to the fact that the plasma cells have a low mitotic index, the obtained metaphases are of low quality and are difficult to analyze. Using conventional cytogenetic it is possible to prove aberrations, distinctive for therapy-related myelodysplastic syndrome (MDS), but this is not a susceptible method for determining genetic abnormalities in the cases with MM. [3] An evidential method for cytogenetic diagnosis in MM is the interphase fluorescent in situ hybridization (iFISH).

Both primary and secondary cytogenetic abnormalities can influence disease course, response to therapy and serve as relevant prognostic factors in MM. Risk stratification of patients with MM is important to predict survival and define a treatment strategy [4]. Patients with MM can be categorized into hyperdiploidy (HD) and non-hyperdiploidy (NHD)

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groups according to the primary cytogenetic abnormalities. Translocations t(4;14), t(14;16) and t(14;20) have been associated with poor prognosis, and their presence identifies high-risk (HR) disease. On the other hand, patients with t (11;14), t(6;14) and/or trisomies are considered to have standard-risk (SR) disease [5,6].

Hyperdiploid multiple myeloma can be observed in around half of the MM patients and is considered as a favorable prognostic factor. The term is used for cases with recurrent trisomies involving odd-numbered chromosomes with the exception of chromosomes 1, 13, and 21. Most patients with HD MM have an indolent course of the disease with a median OS of 7-10 years. They usually present with myeloma bone disease at diagnosis and show an excellent response to lenalidomide-based therapy Trisomies plus any one of the IgH translocations may ameliorate adverse prognosis conferred by high risk IgH translocations and del 17p [7].

More precise estimation of prognosis in MM requires an assessment of additional risk factors - host characteristics, tumor burden (stage), biology (cytogenetic abnormalities), and response to therapy [7]. Tumor burden in multiple myeloma has traditionally been assessed using the classic Durie-Salmon Staging (DSS) [8] and the International Staging System (ISS), which is based on two routinely obtained laboratory parameters – serum b2 microglobuline and albumin [9]. The Revised International Staging System (RISS) combines elements of tumor burden (ISS) and disease biology (presence of high-risk cytogenetic abnormalities or elevated lactate dehydrogenase level) to create a unified prognostic index [10].

During the past two decades significant progress in the treatment of multiple myeloma was achieved, particularly with the use of the proteasome inhibitor (PI) bortezomib and the immunomodulatory agents (IMiDs) thalidomide and lenalidomide. Despite therapeutic advances multiple myeloma remains an incurable disease and outcomes are heterogeneous. Initial treatment strategies in MM depend on the patient's ability to tolerate intensive treatment. Transplant-eligible patients (aged <70 years, without comorbidities) are treated with induction therapy, high-dose chemotherapy, and autologous stem cell transplant (ASCT), followed by maintenance, whereas elderly patients and those with significant comorbidities receive dose-adapted combinations of anti-myeloma agents [11]. Induction therapy utilizing novel agents results in higher response rates post-induction and post-transplantation.

In the last decade numerous agents have been approved by the Food and Drug Administration (FDA) and European Medical Agency (EMA) for the treatment of newly-diagnosed and relapsed/refractory multiple myeloma, and promise to improve outcomes further: proteasome inhibitors (carfilzomib, ixazomib), immunomodiulator (pomalidomide); monoclonal antibodies (elotuzumab, daratumumab, isatuximab), antibody-drug conjugate (belantamab mafodotin), the selective inhibitor of nuclear export selinexor and chimeric antigen receptor T (CAR-T) cell therapies. Numerous combinations have been developed containing 3 (triplets) or 4 (quadruplets) anti-myeloma agents. Furthermore, poor outcomes associated with HR cytogenetic groups, have led to efforts to identify treatments and combinations with the potential to improve prognosis of patients with these abnormalities [7]. Certain abnormalities may influence response to various treatments including novel agents: patients with trisomies may benefit from IMiD-based combinations, while patients with IgH translocation may have better responses to PI-based treatment [12].

2. Material and methods

A FISH analysis of the bone marrow of 26 patients (12 female and 14 males with an average age of 67 years) with newly diagnosed MM using in parallel the following FISH probes: XL 1p36/1q25 del, XL14q32 Break apart and XL 5p15/9q22/15q22 Hyperdiploidy of MetaSystems (Germany) was conducted. Based on the results from the iFISH two subgroups have been formed - with and without clonal aberrations respectively. The demographic data (sex and age), some laboratory parameters (total protein (TP), albumin, lactate dehydrogenase (LDH), beta-2 microglobulin (B2M), and immunoglobulin isotype) and the ISS staging were examined [9]. The diagnosis of MM was made according to the revised diagnostic criteria of the International Myeloma Working Group (IMWG), 2014[13]. All the patients have signed an informed consent form for conducting the procedures needed. All the examinations have been performed according to the instructions of the manufacturers, the standard operating protocols, and the rules for good laboratory practice.

3. Results

Clonal cytogenetic aberrations were proven in 46% (n=12/26) of the analyzed patients. Presence of only HdMC was confirmed in 23% (n=6/26) of all the bone marrow samples. In one of the cases HdMC is in a combination with an additional long arm of the first chromosome (double hit), in 15% (n=4/26) the three FISH probes showed aberration (triple hit). Only one of the cases had 14q32 rearrangement, in that case further analysis was conducted to clarify the

chromosomal partner. Two groups of patients were identified using the result from the iFISH analysis – with and without abnormalities.

The subgroup of MM with clonal aberrations consists of twelve patients (n=12)- 6 women and 6 men with an average age of 72.2 years and there were the following pathological findings in it – HdMC n=6 (50%), double hit n=1 (8%), triple hit n=4 (34%) and 14q32 rearrangement n=1 (8%) (Fig1).

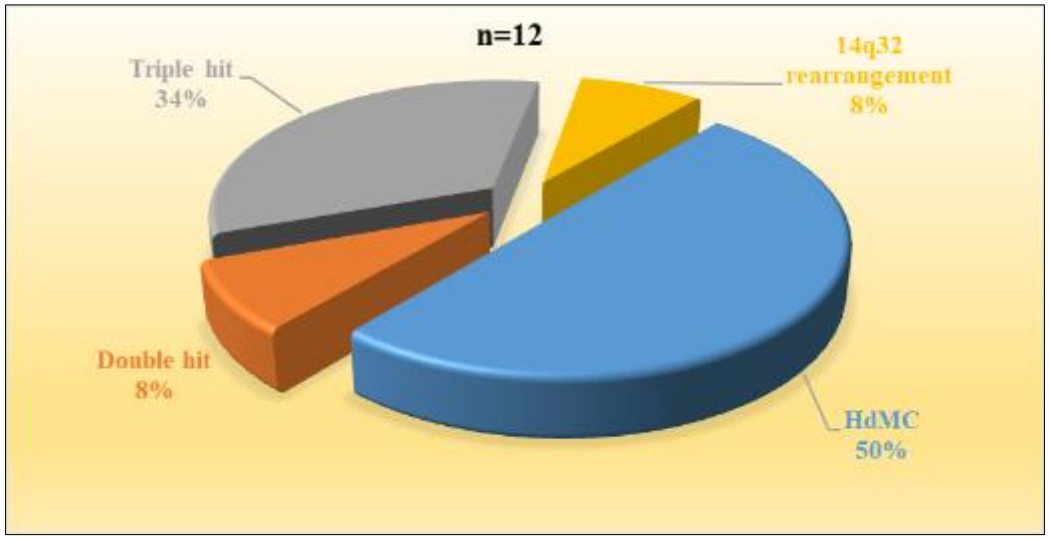

Figure 1 Distribution of genetic disorders in the clonality subgroup

The clonality HdMC varied from 10 to 70%, most frequently it related to an additional chromosome 15 n=10, an additional chromosome 5 and 9 n=9. Regarding the number of copy – trisomy of chromosome 5 n=8, trisomy of chromosome 9 n=6, tetrasomy of chromosome 15 n=5 and tetrasomy of chromosome 9 n=3. The laboratory data showed increased levels of: B2M n=9, total protein n=5, LDH n=4. Serum immunoelectrophoresis defined the monoclonal protein type as isotype IgG/K n=7, IgG/L n=4 and IgA/K n=1 and patients were staged ISS 2 n=6 and ISS 3 n=6.

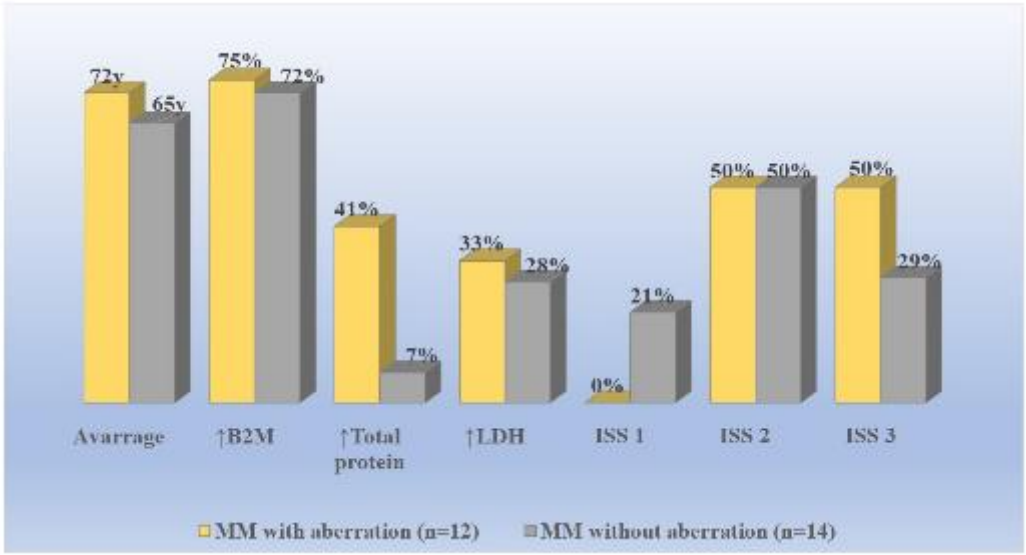

Figure 2 Comparison of demographic, laboratory, and clinical data

In 54% (n=14) of the analyzed samples no chromosome aberrations were detected with the used FISH probes. They represent the subgroup of MM without chromosomal anomalies which consists of 6 women and 9 men with an average age of 65.7 years. The deviations from the laboratory results were as follows: increased levels of B2M n=10, total protein

n=1 and LDH n=4. The monoclonal protein type was IgG/K n=8, IgG/L n=4 and IgA/K n=2, and staging - ISS1 n=3, ISS2 n=7 and ISS3 n=4.

A comparison of the demographic, laboratory data and the ISS staging between the two groups was made (Fig2.).

The subgroup with clonal aberrations was with a higher average age, we found an increase in the B2M, total protein and LDH, and these patients were diagnosed in second or third stage according to ISS. No relation was confirmed between the clonal anomalies and the sex of the patients, respectively the isotype of the serum paraprotein.

4. Discussion

The benefits of the molecular cytogenetics such as the FISH technique have been proven and they give the opportunity for a better understanding of the exceptional heterogeneity of MM not only regarding its genetic manifestations but also the clinical ones. In the current research the percentage of identified clonal anomalities using FISH is lower (46%) compared to the data of most authors – 50 to 90% [14], due to the fact that it was only based on three FISH probes. We confirm the data regarding the frequency of HdMC - 50% from all of the pathological findings in the cases of MM, similar to ~~an~~other scientific research [15]. However, there is a difference when it comes to the affected chromosomes in the cases of HdMC. Some author, similar to us, find a trisomic state of chromosome 15 [16], while others report a trisomy in chromosome 9 [15]. The interesting cases are those with double or triple hit. They show that the presence of HdMC does not exclude another genetic event. There is still not enough data on the more copy number of chromosomes - tetrasomic and/or pentasomic conditions. Like other researchers we did not find a relation between the cytogenetic findings and the isotype of the serum paraprotein. The use of the FISH probe XL 5p15/9q22/15q22 Hyperdiploidy increases the probability of detecting a pathological clone in the cases of MM by 23% which changes the prognosis and the possible therapeutic approach.

Hyperdiploid patients are considered standard-risk and sufficient amount of data show that they benefit from IMiD-based combinations due to higher cereblon-binding proteins expression levels [17,18]. The risk-adapted approach is to use a lenalidomide-based triplet initial therapy (VRd, DRd), ASCT in eligible patients, followed by lenalidomide maintenance. In selected standard-risk patients responding well to therapy, ASCT can be delayed until first relapse provided stem cells are harvested early in the disease course. In high-risk patients PI-based induction and maintenance are recommended and risk-adapted therapy guidelines even favour quadruplet regimens frontline (Dara-VRd) [7].

5. Conclusion

Despite the small scope of our research, the data presented by us proves the advantage of using 5p15/9q22/15q22 Hyperdiploidy FISH probe in the routine laboratory practice when diagnosing MM. Some distinctive deviations in the presence of HdMC have been noticed, but they might be due to the different pathogenetic mechanism. Our findings show the need of a wider ranged research of this myeloma type, looking for innovative approaches and a better management of the disease.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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