EDITORIAL

Relevance of newly acquired mutations to the prognosis of patients with relapsed multiple myeloma

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The complex genetic heterogeneity, expressed at both interpatient and individual levels, is the driving force behind the natural evolution and the treatment response in multiple myeloma (MM). Large-scale studies have demonstrated that certain cytogenetic mutations, such as chromosome 17p deletion (del[17p]), t(4;14), t(14;16), or 1q gain, noted at the time of diagnosis represent high-risk cytogenetic features and are correlated with a worse prognosis in terms of progression-free survival (PFS) and overall survival (OS). Although acquired structural changes are a common feature at relapse, little is known about the impact of the genetic evolution on the treatment response and progression of MM. The emergence of genetically altered clones is the result of Darwinian evolution under the selective pressure exerted by treatment. Chromosome 17p deletion is considered a high-risk feature in newly diagnosed MM and can be observed through fluorescence in situ hybridization (FISH) evaluation in 10% to 20% of patients, depending on the cutoff used. The loss of the short arm of chromosome 17 is correlated with *TP53* tumor suppressor gene silencing. Usually, it is a secondary event in the evolution of MM, but the currently existing data are inconclusive as to whether the subsequent occurrence of del(17p) bears the same unfavorable impact as in newly diagnosed patients.

In the current issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Salomon-Perzyński et al[1] retrospectively analyzed the occurrence of cytogenetic evolution using an interphase FISH test for t(4;14), t(14;16), and del(17p) on magnetically selected CD138-positive plasma cells. Among the 650 patients evaluated in the Warsaw Department of Hematology between 2014 and 2019, the authors selected 177 who had a complete set of data. Out of these, 29 patients with MM had serial FISH testing at diagnosis and relapse. Cytogenetic evolution was defined as the acquisition or loss of a cytogenetic abnormality at the second FISH testing and was observed in 14 patients (48%). Chromosome 17p deletion was identified as the most common acquired feature, found in 7 out of 29 patients (24%), with an established FISH cutoff of 7%. The presence of cytogenetic evolution had a negative impact on PFS, with a median PFS of 3.9 months in patients with cytogenetic evolution versus 9.3 months in those with stable cytogenetics. Univariate and multivariate analyses identified del(17p) as a predictor of shorter PFS and OS. Patients who acquired del(17p) during the course of the disease achieved a significantly shorter PFS of 1.5 months compared with those who did not acquire del(17p) and achieved PFS of 8.9 months. In univariate analysis, stable cytogenetics predicted longer OS of 3.8 years, whereas patients with cytogenetic evolution had an OS of 3.1 years.

Some of the limitations of the study by Salomon-Perzyński et al[1] were acknowledged by the authors and include the retrospective design of the study, the limited number of participants, and the fact that the patients were not treated uniformly, having little access to novel antimyeloma drugs.

Another caveat is the fact that the authors did not separately evaluate the occurrence of cytogenetic evolution in the patients tested at the first clinical or biochemical relapse as compared with the ones tested at subsequent clinical relapses. It is a well-known fact that MM evolution is characterized by progressive aggressiveness and lack of response to therapy as the disease unfolds.

The authors stated that the refractory status to proteasome inhibitors (PIs) and / or immunomodulatory drugs (IMiDs) and refractoriness to the last treatment line before the second FISH

evaluation were not significantly correlated with the occurrence of cytogenetic evolution. In addition to the impact of acquired del(17p) on PFS and OS, it would be relevant to evaluate the changes observed in these patients regarding the treatment response rate and depth. Current data suggest that MM relapse is characterized by emergence of treatment-resistant subclones. Interestingly, the authors also did not find any significant correlation between the response to the last treatment line and cytogenetic evolution. Large-scale studies showed that the depth of the treatment response is the most important determinant of the evolutionary pattern seen at relapse. Patients achieving a deeper response show a branching evolution model, with both gain and loss of mutational clusters. More modest responses are correlated with a linear evolution, defined only by gain of mutations or with a stable mutational pattern.[2]

Despite the relatively small number of patients, the study provides relevant data about the key role that cytogenetic instability, del(17p) in particular, plays in the natural evolution of MM. Although the gain of cytogenetic abnormalities have been shown to be involved in disease progression, little is known as to whether they have the same prognostic significance as the high cytogenetic risk features identified in newly diagnosed patients with MM.

Most accurate data regarding genetic evolution in MM come from mass next-generation sequencing testing in the large clinical trial settings. Since FISH testing is the commonly used technique in most clinical centers, it is of value to correlate the results extracted using these 2 different techniques.

Although some studies identified 1q gain as the most common new event at relapse, and others showed that the most prevalent genetic alterations are del(17p), monosomy 13, trisomy 11, and tetrasomy 15, there seems to be an agreement that del(17p) accounts for 10% of the cytogenetic evolution events.[3-6] Moreover, the gain and loss of the structural lesions, del(1p), del(13), del(14), del(17p), and gain (1q) at relapse were more common in patients achieving complete response (CR) compared with non-CR patients.[5,6]

The study by Salomon-Perzyński et al[1] confirmed the findings of published reports, namely, the fact that acquired del(17p) has a strong impact on both PFS and OS. Studies using longitudinal FISH analysis proved that the occurrence of del(17p) after diagnosis is correlated with a significantly worse outcome.[7-9] However, current data suggest that, in patients surviving more than 3 years, the negative prognostic impact caused by the presence of high-risk cytogenetic features becomes less pronounced.[7]

Although some authors identified hyperdiploidy, high levels of LDH, or the presence of t(4;14) at diagnosis as a risk factor for developing subsequent cytogenetic aberrations, there is still a debate surrounding the existence of predisposing factors. Nevertheless, it seems that patients relapsing after being exposed to novel agents and autologous stem cell transplant appear to be at greater risk of developing additional high-risk cytogenetic features. This effect can probably be explained by the fact that these patients achieve a deeper level of response and that treatment acts like a bottleneck for the emerging treatment-resistant subclones.[10] The proneness towards evolving cytogenetics in patients exposed to novel agents is another argument for including routine FISH testing at relapse in order to ensure the optimal treatment choice in these patients. The study by Salomon-Perzyński et al[1] offers crucial insights into the significance of sequential FISH testing in understanding the natural evolution of MM and as a step towards adapting an optimal therapeutic strategy. There is less consensus regarding the risk stratification of patients who acquire del(17p) later in the disease course. The data presented by Salomon-Perzyński et al[1] support the existing evidence of the negative impact that loss of chromosome 17 has on OS and PFS in patients with MM. Future analysis should focus on determining whether there is any correlation between the acquisition of del(17p) and the time to progression. Also, there is still a knowledge gap regarding the cutoff for the FISH analysis for del(17p). Future prospective studies are needed to optimize therapy in this subset of patients, particularly in correlation with the response to the previous line of treatment. New therapeutic strategies should be designed for these patients by incorporating data on the acquired mutational burden, time to progression, and response to the previous line of therapy, since early relapses are caused by primary therapy resistance, with no significant changes in the clonal genetics, and patients that achieve a CR / minimal residual disease negativity show profound chromosomal alterations at relapse.

Despite a considerable progress in research, MM remains an incurable disease and its relapse is inevitable, although the introduction of novel therapies significantly improves survival. The current paradigm evolves towards establishing a personalized treatment for the patient with MM. To this end, sequential cytogenetic testing at diagnosis and subsequent relapses could provide the necessary scaffolding for adapting therapy and achieving the best possible response.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

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