Scientific Comment

Comment on: “Validation of interphase fluorescence in situ hybridization (iFISH) of CD138 positive cells in multiple myeloma”

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A R T I C L E  I N F O

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Genetic studies play a central role in the study of multiple myeloma (MM), as they are a critical component in the risk-based classification of the disease. Significant effort has been made to identify and include genetic markers in the routine clinical care. The work by Kishimoto on interphase fluorescence in situ hybridization (iFISH) of purified CD138 cells is an example of such effort.

iFISH in purified plasmatic cells is one of the most used techniques in the clinical practice due to its straight forward implementation and simplicity of data analysis. iFISH is today the standard tool to detect genetic abnormalities and for disease prognostication.

It is worth mentioning that other genomic–transcriptomic techniques used in the risk-based classification of MM patients such as comparative genomic hybridization (aCGH), next generation sequencing (NGS) and gene expression profiling (GEP or RNAseq), also need to be performed in purified MM cells to ensure accurate results. This fact makes Kishimoto’s article of the utmost importance.

Genetic classification of multiple myeloma

MM is a hematological malignancy characterized by an abnormal accumulation of clonal plasma cells (PC) in the bone marrow (BM). Genetic alterations are observed from the early stages of the disease and are key events in the establishment of the clonal PC population. Genetic alterations have been used as a basis to classify the disease and patients into different prognostic groups and, more importantly, may be used in the near future as predictive markers of therapeutic response.

The Mayo Clinic proposed a simplified genetic based classification (mSMART) which segregates patients into three prognostic groups: high, intermediate and standard according to genetic alterations. High risk MM is characterized by del(17p), t(14;16) and t(14;20); intermediate by t(4;14), 1qgain, complex karyotype, hypodiploidy or metaphase detected del13, while standard risk MM is characterized by all other aberrations including trisomies (especially of chromosomes 3,
5, 7, 9, 11, 15, 19, and 21), t(11;14) and t(6;14). With the exception of the chromosome 13 deletion which shows prognostic value only if detected by cytogenetics; all other alterations are best evaluated by FISH.²

It seems that FISH will remain the standard technique to detect alterations and subsequent stratification of MM into differentiated risk groups until genomic analysis becomes easy to interpret and cheaper. A recent review from the International Myeloma Working Group (IMWG) pinpointed three specific aberrations, namely the IGH/FGFR3 fusion gene, 1q21gain, and TP53 loss, as markers to stratify high-risk MM patients at diagnosis and recommend their use in the routine practice.³

Two points should be emphasized regarding the genetic changes that drive risk stratification of patients with MM. The first is that the single most important genetic prognostic factor in MM, irrespective of treatment, the del(17p) [TP53 mutation], is not an early event in MM pathogenesis and is more commonly detected during progression. The other is that the clonal architecture of MM at diagnosis is characterized by multiple clones and shift during progression mainly due to therapy. This may imply that prognostic evaluations need to be performed not only at diagnosis but also during treatment.

Finally, it is worth noting that the current genetic classification is based on patients treated with chemotherapy associated or not to autologous transplantation. New therapies based on proteasome inhibitors, immunomodulators (IMiDs) and target-specific drugs are being introduced. Whether this same set of genetic alterations will be sufficient to individualize therapy for MM patients in the context of proteasome inhibitors and IMiDs remains to be defined.

**Alternative methods for detecting genetic alterations in multiple myeloma samples**

aCGH is an alternative technology to test copy number variations that may gain a place in MM genetic stratification in the near future. The use of an oligonucleotide 8 × 60 K aCGH platform complemented with iFISH for t(4;14)[IGH-FGFR3/MMSET] has recently been described for the routine diagnostic setting of MM patients.⁴

While this approach is vulnerable in detecting small and low numbers of clonal alterations at the TP53 locus when compared to iFISH, it was more effective in detecting cryptic losses within the IGH region [14q32]. It was suggested that this approach was cost neutral when compared with FISH screening and offers the advantage of a whole genome scan.

Then again, there are suggestions that the use of gene expression profiles (GEP) as a technique to detect translocations in the detection of the 17p deletion may replace iFISH as a tool for risk stratification in MM. Finally, next generation sequencing, if included in the MM evaluation, may reveal modifications in important actionable targets such as KRAS, NRAS, BRAF, FGFR3, CCND1, IDH1, and IDH2.

Nevertheless, until high-resolution techniques are ready to enter the clinical practice, FISH will probably continue to be the best tool to establish a prognosis for MM patients.

**Conflicts of interest**

The author declares no conflicts of interest.

**References**

1. Mayo Clinic. Available from: www.msmart.org [accessed 03.03.16].