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Editorial Open Access

Assessing MYC Expression in Multiple Myeloma

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Editorial

Multiple myeloma (MM) is characterized by clonal proliferation of neoplastic plasma cells that secrete monoclonal immunoglobulin or M-protein. Prognosis in multiple myeloma is influenced not only by staging and patient factors but also by disease biology [1]. Conventional cytogenetic studies and fluorescent in situ hybridization (FISH) are widely used currently to identify cytogenetic abnormalities and stratify MM into high risk, intermediate risk and standard risk categories as shown in Table 1.

Standard-risk
Trisomies
t (11;14)
t (6;14)
Intermediate-risk
t (4;14)
Deletion 13 or hypoploidy
High-risk
17p deletion
t (14;16)
t (14;20)
High risk signature on gene expression profiling

Table 1: Risk stratification in multiple myeloma [1].

Recently, MYC gene related dysregulations, MYC over-expression and its role in prognosis has been studied in MM. MYC is a regulator gene located on chromosome 8 and it encodes for a transcription factor which plays a major role in cellular proliferation. MYC gene rearrangements in association with t (8;14), t(8;22) and t (2;8) has been originally studied in 90% cases of Burkitt lymphoma [2]. Chng et al. reported that MYC over-expression was related to poor prognosis in MM. This study also concluded that MYC activation is playing a role in transformation of monoclonal gammopathy of undetermined significance (MGUS) to MM. They found that MYC was activated in 67% of newly diagnosed MM cases but not in MGUS [3]. But however, this study did not focus on the MYC gene related abnormalities including translocations and gene amplifications (GA).

More recently Sekiguchi et al. retrospectively analyzed the impact of MYC gene related abnormalities and aneuploidies of chromosome 8 on prognosis using conventional karyotyping and FISH in newly diagnosed MM [4]. They performed conventional cytogenetic analysis using G-banding method to classify hyperdiploidy (HD) and non-hyperdiploidy status (N-HD). FISH analysis was performed to detect major cytogenetic abnormalities like del13q, IGH/BCL, IGH/FGFR3, del p53, IGH/MAF1, IGH/MYC, MYC translocations other than IGH and MYC GA. People who harbor N-HD, IGH/FGFR3, del 17p and IGH/MAF1 were classified as high risk group and those who do not carry the above abnormalities were stratified to standard risk group. Cytogenetic analysis was performed on 33/40 patients and 15/33 (45.5%) were classified as high risk group. IGH/MYC, MYC GA, MYC gene translocations other than IgH gene and additional chromosome 8 were identified in 2, 6, 1 and 4 patients on diagnosis respectively. However, the above mentioned translocations and MYC GA were equally distributed between high and standard risk groups. Median follow-up duration was 13.3 months. 17 patients died and 14 patients had Relapsed/Refractory Multiple Myeloma (RRMM).

They found that more patients with MYC gene-related abnormalities developed RRMM (77.7%). There was no significant difference in overall survival (OS) and progression free survival (PFS) between high risk and standard risk groups. When individual risk factor influence on survival was looked at, N-HD, IGH/FGFR3 and del p53 did not affect PFS or OS. Interestingly, people who had MYC gene related aberrations trended in inferior PFS when compared to those who did not have gene abnormalities (19 months vs. not reached, P=0.08). Also the study found that people who had MYC aberrations and/or additional chromosome 8 had significantly shorter PFS (24 months vs. not reached, P=0.03). This study has shown that MM patients who have MYC gene related aberrations have a poor prognosis.

Our group has retrospectively analyzed MYC expression in plasma cells using immunohistochemical staining in 26 patients with newly diagnosed MM and 29 patients with MGUS [5]. We have evaluated bone marrow core biopsies from 26 newly diagnosed MM patients, 29 patients with MGUS, 5 patients with polytypic plasmacytosis, 20 cases of lymphoplamocytic lymphoma (LPL), 21 cases of marginal zone lymphoma (MZL), 5 cases of IgG4-related sclerosing disease and 9 cases of plasmablastic lymphoma (PBL).

Nuclear MYC expression was detected in 22 of 26 MM cases with CD-138- positive plasma cells (84%). Among those 22 patients, 8 had >70% MYC-positive plasma cells, 9 had 30% to 70% MYC- positive plasma cells and 5 had 1% to 30% MYC-positive plasma cells. Interestingly, all the 29 patients with MGUS had no MYC expression.

These 26 cases of MM were divided into low-MYC-expressing (MYC<30%, 9 patients) and intermediate to high-MYC-expressing (MYC ≥ 30%, 17 patients) groups. There was no significant difference in distribution of sex, age, cytogenetic risk factors, staging, immunoglobulin type, light chain restrictions, anemia, renal failure, hypercalcemia and elevated β-2-microglobulin levels between the two groups. All patients with >10% Ki67 proliferation index were present

in the intermediate to high-MYC-expressing-group. We have also evaluated 18 follow-up biopsies in 8 patients with high MYC expression and found that MYC was detected in all patients with residual disease even in those with <5% plasma cells.

All 26 MM patients received chemotherapy with bortezomib and 21 (81%) underwent high dose chemotherapy with autologous stem cell transplantation (SCT).

In the low-MYC-expressing-group, 1/9 patients had disease progression/relapse compared to 8/17 patients in the intermediate to high MYC-expressing-group. Also, 5/17 patients in the intermediate to high-MYC-expressing group died and no deaths were observed in low MYC-expressing-group. The 24-month PFS was significantly shorter in patients with intermediate to high MYC-expressing-group when compared to low MYC-expressing-group (40% vs. 86%, P=0.0237). However, OS was not significantly different in the two groups. There was also a trend towards better survival among patients who underwent SCT (OS 87% vs. 62%, P=0.079). Of note, 5/8 patients who developed MM from MGUS gained MYC expression on follow-up bone marrow biopsies.

Together with the data from above studies MYC gene aberrations/MYC protein may serve as a useful predictor for prognosis and also to assess residual disease.

We believe that MYC protein expression is easily assessed by immunohistochemistry while conventional cytogenetics and or FISH can be laborious, expensive and not as broadly available. We suggest that testing for MYC expression should be done at the time of diagnosis along with other prognostic markers and it may also have a value during the course of treatment as a marker for minimal residual disease (MRD).

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