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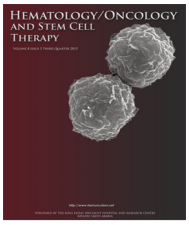

BRIEF COMMUNICATION

Presence of fluorescent *in situ* hybridization abnormalities is associated with plasma cell burden in light chain amyloidosis

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Abstract
Objective/Background: To assess abnormalities found on CD138-enriched fluorescent *in situ* hybridization (FISH) studies on pre-treatment bone marrow in systemic amyloid light-chain amyloidosis (AL) and correlate findings between these abnormalities with organ involvement and 1-year survival.
Methods: We reviewed 107 patients with systemic AL to identify the impact of a diagnostic FISH study done on plasma cell-enriched bone marrow in our institution between January 2010 and January 2015; 77 had pre-treatment testing performed.
Results: A total of 77 (61%) patients had abnormal FISH including: hyperdiploidy (29%), t(11;14), (20%), hypodiploidy (16%), t(4;14), (1%), del17p (5%), and + 1q21 (5%). Abnormal FISH studies were more likely in those patients with plasma cell involvement $\geq$ 10% (p = .002). FISH abnormalities were not shown to correlate with stage, cardiac involvement, or survival at 1 year. One-year survival was significantly affected by stage at diagnosis and presence of cardiac and hepatic amyloid involvement.
Conclusion: We conclude that in AL, FISH abnormalities are associated with clonal burden. We found no impact of these markers on the type of organ involvement or 1-year survival.

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Introduction

Immunoglobulin light-chain amyloidosis (AL) is a plasma cell neoplasm in which clonal immunoglobulin light chains, either lambda (λ) or kappa (κ), misfold into insoluble fibrils (amyloid) and deposit in tissues [1]. The pathogenesis of AL depends on the degree of systemic deposition of amyloid fibrils into vital organs, ultimately disrupting their functioning [2]. Because AL amyloidosis shares a plethora of chromosomal abnormalities with the more common plasma cell neoplasm, multiple myeloma (MM), and because the two can coexist, molecular markers in MM are of interest in AL amyloidosis. Both AL amyloidosis and MM have been found to have similar, frequently occurring translocations such as t(4;14), t(11;14), t(14;16), deletions such as del13/del13q, del17p, and aneuploidy [3,4]. Using fluorescent *in situ* hybridization (FISH) coupled with cytoplasmic staining of a specific immunoglobulin, researchers have studied the genetic similarities between AL and MM but associated with differences in frequency and prognosis [3]. Others have shown that certain markers associated with high risk in MM-t(4;14), del17p, del1q, and hypodiploidy-can also produce a ''high-risk" AL phenotype and poor prognosis [5]. We analyzed FISH abnormalities seen in clonal plasma cells in our institutional series of AL patients. Our objectives were to characterize these clonal abnormalities, find associations with patient and AL amyloid disease characteristics, and assess if the presence of certain markers changed early AL prognosis.

Methods

This Institutional Review Board-approved, retrospective cohort study identified 107 patients with newly diagnosed systemic AL seen at a tertiary academic medical center between January 2010 and January 2015; these patients were included in this analysis and related data were analyzed. AL subtype was confirmed with mass spectrometry-based proteomic subtyping after 2011 [6].

Demographic factors, baseline laboratory, and pathology information were collected. Molecular markers were identified as follows: CD138-enriched FISH panels for MM and cytogenetics from bone marrow were collected for those patients who had them. Most FISH studies were done at our institution. High-risk FISH markers were defined according to the MM literature as any one or more of the following: t(4;14), t(14;16), t(14;20), del17p, +1q21, and hypodiploidy. The presence of t(11;14) and other abnormalities such as monosomy 13 and hyperdiploidy was also recorded. Bone marrow clonal plasma cells (BMPCs) were grouped into either ''<10%" or ''≥10%," defining ≥10% plasma cells as a coexistent MM. Organ involvement from AL amyloidosis was recorded. Organ involvement was characterized as ''cardiac," ''renal," ''hepatic," ''peripheral neuropathy," ''autonomic neuropathy," and/or ''soft tissue" based on biopsy, biomarker, and imaging studies [7]. The cardiac stage was calculated using the 2004 Mayo Clinic Staging criteria [8]. Thirty-five of 107 patients did not have baseline N-terminal pro B-type natriuretic peptide and/or troponin T to calculate cardiac stage. A cutoff of ≥10% plasma cells was used to denote coexistent MM based on International Myeloma Working Group criteria [9].

Statistical analysis

Using univariate analysis, FISH markers were correlated with age at diagnosis, sex, race, organ involvement, cardiac stage, percent clonal plasma cells, and 1-year survival. One-year survival analysis was performed, with patients censored after 1 year from diagnosis. The following variables were tested in the survival analysis: age at diagnosis, sex, race, molecular markers, percent clonal plasma cells, 2004 AL stage, and cardiac, renal, and hepatic involvement. Owing to a small number of events at 1 year, a multivariate analysis was not feasible in this cohort. A p value <.05 was considered statistically significant and analysis was preformed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Patients had a median age of 67.4 years (range, 35.1–91.1 years) at diagnosis and 55 (51%) were women (Table 1). Seventy-seven patients (72%) reported FISH studies and results in 46 patients (61%) were abnormal. There were 34 (32%) patients with BMPCs ≥10%. The median follow-up time of survivors was 21.2 months (range, 0.7–83.3 months).

FISH abnormalities

Of the series, 77 patients had FISH studies performed on a diagnostic bone marrow, with abnormalities seen in 46 (61%). The frequencies of individual abnormalities are shown in Table 1. As much as 32% of patients had abnormalities involving immunoglobulin heavy chain (IgH). Other specific abnormalities included t(11;14) (20%), t(4:14) (1%), del17p (5%), and +1q (5%). The most common abnormality overall was hyperdiploidy (29%), followed by t(11;14) (14%) and monosomy 13 (17%). Univariate analysis showed no association between individual abnormalities with sex, race, cardiac involvement, or 1-year survival. However, presence of a FISH abnormality was correlated with a higher plasma cell burden, that is, coexistent MM (p = .0016) and MM ''high-risk" abnormalities-t(4;14), del17p, +1q, or hypodiploidy; additionally, chromosomal repeats (either polysomy 11 or hyperdiploidy) showed a positive correlation with ≥10% BMPCs (p = .046 and p = .004, respectively; Fig. 1).

One-year survival and prognosis

Survival analysis at 1 year is shown in Table 2. Presence of cardiac involvement correlated with decreased survival (p = .02) as did AL amyloid Stage III (p = .002). Presence of hepatic AL involvement also correlated with decreased 1-year overall survival (p = .02). The presence of cardiac involvement was associated with a survival probability of 73.1% (95% confidence interval [CI]: 60.1–82.5) at 1 year

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