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Cytogenetic Features and Clinical Outcomes of Patients with Non-Secretory Multiple Myeloma in the Era of Novel Agent Induction Therapy

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Abstract

Background: Non-secretory multiple myeloma (NSMM) is a rare subtype of multiple myeloma (MM) characterized by the absence of monoclonal protein in the serum and/or urine. We look at the clinical and cytogenetic features of NSMM in this study.

Patients and Methods: This study evaluates a cohort of 30 patients with newly diagnosed NSMM seen at the Mayo Clinic, Rochester between 2008 to 2018 and treated with novel agent induction therapies. Survival outcomes were estimated using the Kaplan-Meier method and compared using log rank test.

Results and conclusions: These patients with NSMM appear to have a large disease burden at diagnosis with a median bone marrow plasma cell percentage of 70% and more than half of all patients having ISS Stage III disease. There was a higher preponderance for t(11;14) primary cytogenetic abnormality in this NSMM cohort accounting for more than 50% of the cohort. Finally, the overall survival (OS) of this cohort appears to be slightly worse than a matched-control group of newly diagnosed MM patients with secretory disease. Future multi-institution studies confirming these above findings on this rare entity are warranted.

MICROABSTRACT:

Non-Secretory multiple myeloma is a rare form of multiple myeloma characterized by the absence of a monoclonal protein in serum and urine. This study looks into the clinical and cytogenetic

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features of this disease. The study cohort consisted of 30 patients diagnosed between January 1st 2008 and December 31st 2018. The study revealed that there was a preponderance of the t (11;14) cytogenetic abnormality in this group of patients. Compared to a control group of secretory multiple myeloma patients, matched for age and year of diagnosis, the non-secretory multiple myeloma had worse survival outcomes but this was statistically insignificant.

Keywords

Non-secretory myeloma; myeloma survival; t (11;14) cytogenetics

INTRODUCTION

Multiple myeloma (MM) is a malignancy of the bone marrow characterized by uncontrolled proliferation of clonal plasma cells along with the production of complete clonal immunoglobulins (comprised of the heavy and light chains bound together) or just the light chains. This allows for monitoring of the disease burden in the serum and/or urine in response to therapy or while off therapy.¹ In contrast, non-secretory MM (NSMM) is a rare subtype of MM characterized by the presence of a negative serum and urine electrophoresis with immunofixation as well as normal serum free light chain (sFLC) levels. NSMM was thought to constitute 3-5% of all newly diagnosed MM.² However, with the advent of the sFLC assay, patients previously considered to be NSMM were found to secrete primarily unbound sFLCs in the absence of the heavy chain making the true incidence of NSMM closer to 1% of all MM. Over the last two decades, the overall survival (OS) of patients with MM has improved with uniform utilization of autologous stem cell transplantation (ASCT) and novel agents such as proteasome inhibitors (PIs) immunomodulators (IMiDs).³ Furthermore, advances in molecular cytogenetics have also led to better classification of MM into different prognostic subsets.⁴ However, details on the clinical features and outcomes of patients with NSMM in the novel agent era and the presence of the sFLC assay are scarce. Thus, we here review the clinicopathologic features and clinical outcomes of patients with NSMM in the era of novel agent induction therapies treated at a single tertiary care institution.

METHODS

A database discovery query builder search of the electronic medical records was performed using the terms non-secretory multiple myeloma to identify patients seen at Mayo Clinic, Rochester, Minnesota during the time period between January 1st 2008 and December 31st 2018. The NSMM group identified for this study was defined as patients with a negative serum and urine electrophoresis with immunofixation, along with an involved serum free immunoglobulin light chain (sFLC) of less than 5 mg/dL. Data regarding these patients were extracted from prospectively maintained databases and a review of their electronic medical records. All patients had consented to the use of their medical records, and the study was conducted in accordance with the institutional guidelines with approval of the institutional review board and in accordance with the principles of the Helsinki Declaration.

Fluorescent *in situ* hybridization (FISH) results, if performed within 6 months of diagnosis, were considered for analysis. Tests with insufficient plasma cells for adequate analysis were not included in the analysis. Patients were considered to have high-risk disease if FISH studies demonstrated one of the following abnormalities: t (4;14), t (14;16), t (14;20) or loss of p53 gene locus (del 17p or monosomy 17) in the absence of any trisomies. Patients with any of the other abnormalities or a normal FISH were considered to have standard risk multiple myeloma. Kaplan-Meier analysis was used for analyzing overall survival (OS), and the differences between the groups were tested for statistical significance using the two-tailed log-rank test.

RESULTS AND DISCUSSION

A total of 30 patients were included in this cohort of NSMM patients. This accounts for 1% of all newly diagnosed MM patients evaluated at our institution during the time period. The median age at diagnosis was 62 years (range: 40-79) with 25 (83%) patients being < 70 years of age and 16 (53%) were male. Table 1 provides additional baseline clinical characteristics of this patient cohort. The median bone marrow plasma cell percentage at diagnosis was 70% (range: 15 – 100). A total of 6 (27%) of 22 patients presented with hypercalcemia and 11 (44%) of 25 patients presented with anemia (hemoglobin < 12 g/dL). There were 3 (12%) of 25 patients who presented with a creatinine of 2 mg/dL or greater. Cross sectional imaging results were available in 25 (83%) patients of which 8 patients had PET/ CT scans that were all positive for FDG avid bone lesions. All patients received novel agent containing induction regimens, with 11 (37%) receiving a PI-based regimen, 7 (23%) received an IMiD-based regimen and 12 (40%) received a PI and IMiD combination regimen (Table 2). A total of 15 (50%) of the patients in the cohort received an upfront ASCT. Out of the 30 NSMM patients, cytogenetic data were available for 28 patients (93%) and the most common genetic abnormality was t (11;14) in 16 (57%) patients. Figure 1A depicts the proportions of different primary cytogenetic abnormalities in NSMM. The median TTNT and OS for this cohort was 38 months and 59 months (95% CI: 34 – 64) respectively. When compared to a control cohort of newly diagnosed MM patients with secretory disease in the serum and/or urine that were matched for age, gender and year of diagnosis (used to account for equal access to therapies available) in a 1:2 ratio, the median OS was worse for the NSMM cohort but this was not statistically significant (59 vs. 92 months, $p = 0.257$) (Figure 1B). The median TTNT for the control cohort was 53 months compared to 38 months in the NSMM cohort. However, these results were statistically insignificant ($p=0.8$). Among patients with NSMM, those with a t(11;14) cytogenetic abnormality had a median TTNT and OS of 34 and 46 months respectively compared to NR and 64 months in patients without a t(11;14) abnormality (TTNT: $p = 0.027$; OS : $p = 0.003$).

This subset of NSMM patients is a challenge to treat in the clinic due to the absence of secreted whole immunoglobulins or light chain components in either the blood or urine making it difficult to monitor disease status and progression while on therapy. Prior to the clinical utilization of the sFLC assay, patients classified as having NSMM likely included patients with light chain secreting MM. In contrast, this study excludes patients with light chain only secreting MM by assessment of the sFLC assay. In this study, the cut-off value for involved sFLC being less than 5 mg/dl was picked instead of just an abnormal involved

sFLC level in order to ensure that our cohort did not exclude those non-secretory patients with moderate to severe renal impairment that led to mild rises in the levels of the involved sFLC level. The biological basis for NSMM is not fully understood but can potentially stem from a defect in either the synthesis of whole immunoglobulins as well as free light chains or in the secretion of these aforementioned paraproteins from within the clonal plasma cells into the serum.^{3, 4} It has been suggested that single amino acid substitutions in the light chain or mutations in the immunoglobulin gene can result in the inability of that plasma cell to secrete either types of paraproteins.⁵ Our study demonstrates a preponderance of t (11;14) detected in the clonal plasma cells of NSMM patients (57%) (Figure 1A) compared to the historic prevalence in newly diagnosed MM patients with secretory disease (~ 10-15%). One other prior study also found that 11 out of 14 NSMM patients contained a t (11;14) genetic abnormality suggesting that more lymphoid nature of the clonal plasma cells in these patients may contribute to the non-secretory nature.^{6, 7} This finding is of critical clinical importance due to high bcl-2 expression in patients with MM who harbor the t (11;14) genetic abnormality and the well documented therapeutic potential of bcl-2 inhibition with agents such as venetoclax.^{8, 9} This study noted a high tumor burden at diagnosis in these patients with a median bone marrow plasma cell percentage of 70% and more than half of the patients have ISS stage III disease. It is possible, but not conclusive, that the lack of detectable paraproteins in the serum and/or urine may delay the diagnosis of MM until proven later by a bone marrow or other histological biopsy. None of the existing single institution or large registry studies looking at patients with NSMM observed a significant impact on the OS of these patients when compared to newly diagnosed MM patients with secretory paraproteins.¹⁰⁻¹³ In contrast, this study demonstrated a non-statistically significant worse OS in the NSMM cohort compared to a matched control group of newly diagnosed MM (NDMM) patients with secretory disease (Figure 1B). One obvious possibility is the lower frequency of high-risk cytogenetics in the control group of secretory MM compared to our NSMM cohort. It is also possible that patients with t(11;14) that comprise majority of the NSMM cohort derive a more modest benefit to proteasome inhibitor-based regimens since over two-thirds of our NSMM cohort received proteasome inhibitor-based induction regimens. However, another possibility for this observation could be that patients with NSMM are mostly excluded from participating on clinical trials evaluating the efficacy of novel therapeutic agents due the difficulty in monitoring disease response

CONCLUSION:

Though this study has several limitations such as lack of serial cross sectional imaging information to monitor therapy response and small sample size of NSMM patients as a result of its rarity, it still provides insight into the clinical presentation, outcomes and cytogenetic features of this population in the era of novel agent therapies. In the future, with the advent of more sensitive technologies such as matrix associated laser desorption ionization (MALDI) mass-spectrometry which is capable of detecting very low levels of circulating paraprotein in the serum and urine unlike traditional electrophoresis and immunofixation methods^{14, 15}, the true prevalence of NSMM may be lower making it an even rarer entity.

ABBREVIATIONS:

MM	Multiple myeloma
NSMM	Non-secretory multiple myeloma
NDMM	Newly diagnosed multiple myeloma
sFLC	Serum free light chains
OS	Overall survival
ASCT	Autologous stem cell transplant
PIs	Proteasome inhibitors
IMiDs	Immunomodulators
FISH	Flourescent in situ hybridization
MALDI	Matrix associated laser desorption ionization

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Clinical practice points:

- NSMM is a rare entity in plasma cell malignancies with an absence of identifiable monoclonal protein in urine and serum.
- There is a higher incidence of t(11;14) cytogenetic abnormality in NSMM than other secretory myeloma making targeted therapies such as bcl-2 inhibition of interest in this rare sub-group..
- Timely diagnosis can be difficult to achieve and monitoring response to therapy is challenging.

FIGURE 1A:
Pie chart delineating the distribution of various primary cytogenetic abnormalities in the cohort of NSMM patients

FIGURE 1B:

Kaplan-Meier Curve comparing the survival of patients with NSMM to a 1:2 matched control group of newly diagnosed MM patients with secretory disease

TABLE 1:

Clinical characteristics of the 30 patients with NSMM diagnosed between 2008 - 2018

	NSMM (N = 30)	NDMM (Control group, N = 60)
Patient characteristics	Median (Range)	Median (Range)
Age(years)	62 (47 - 78)	62(39-79)
Male (N, %)	16 (53%)	33 (56%)
Presenting complaint/symptom (N, %)	Bone lesions: 21 (70%) Hypercalcemia: 3 (10%) Anemia: 5 (17%)	Bone lesions: 35 (58%) Hypercalcemia: 2 (3%) Anemia: 13 (22%)
ISS stage III (N, %)	11 (52%) (available in 22 pts)	15 (38%) (available in 40 pts)
Albumin (g/dL)	4 (3.1 – 4.8)	3.4(2.3-4.2)
β-2-microglobulin (mg/dl)	6.1 (2.3 - 10.4)	5(1.4-19.8)
LDH (IU/dl)	232 (121 - 908)	158(102-1253)
Serum calcium(mg/dl)	9.8 (8.9 - 15.7)	9.8(1.06-16.1)
Serum creatinine(mg/dl)	0.9 (0.8 - 2.5)	1.1(0.6-6.6)
Bone marrow plasma cell %	70 (15 – 100)	46(2-90)
High-risk cytogenetics (N, %)	6 (21%)	2 (5%) (available in 38 pts)
Treatments received (N,%)	PI- 11(37%) IMiD-7(23%) PI+IMiD-12(40%) (Available in 29 pts)	PI-19(35%) IMiD-23(42%) PI+IMiD-15(27%) (Available in 55 pts)
ASCT(N,%)	15(50%)	21(35%)

Abbreviations:

LDH (Lactate dehydrogenase)

TABLE 2.

Treatments received by patients in the NSMM group and control group.

REGIMEN	NON-SECRETORY MM(N,%)	NDMM(CONTROL GROUP)(N,%)
VRD (bortezomib, lenalidomide and dexamethasone)	12(40%)	14(25%)
CyBorD (cyclophosphamide, bortezomib and dexamethasone)	8(28%)	9(16%)
Other bortezomib-based regimens	2(6%)	13(27%)
Thalidomide-dexamethasone	1(3%)	1(2%)
Lenalidomide-dexamethasone	7(24%)	20(36%)