



Is Paraproteinemia More Prevalent in Patients with Chronic Myeloid Leukemia?

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OBJECTIVES

- Though originating from different cell origins, several reports have described patients with the coexistence of chronic myeloid leukemia (CML) and paraproteinemias, mostly in patients treated with tyrosine kinase inhibitors (TKIs).
- Objective: To determine whether the prevalence of paraproteinemia in a large cohort of chronic phase (CP-) CML patients is higher than expected in the general population.

METHODS

- A cross-sectional study among out-patient CP-CML patients treated in a tertiary medical center.
- Between February 2019 and May 2021 consecutive CP-CML patients who consented to the study, performed the following tests: complete blood count, routine chemistry, BCR-ABL1 PCR level, quantitative immunoglobulin (Ig) levels, serum-free light chains (sFLC), serum protein electrophoresis (SPEP), and if abnormal also serum protein immunofixation (IFIX).
- The primary outcome was the prevalence of paraproteinemia among this cohort of CML patients.
- Further analyses was done to evaluate whether various patient, disease and treatment-related variables are predictors of paraproteinemia within our cohort.
- Anemia - defined according to the World Health Organization criteria as hemoglobin level <12 g/dL & < 13 g/dL for females & males, respectively.
- The study was approved by the Institutional Review Board.

RESULTS

- A total of 106 patients were recruited. Data for analysis was available in 100 of them: median patients' age was 63.5 (range 26-91.6) years, 50% males. Most patients enrolled were treated with a 1st line treatment (n=62), while others were in their 2nd line (n=24), 3rd line (n=11), and 4th line (n=3) of treatment.
- **A monoclonal protein was detected on serum electrophoresis and immunofixation in 8 patients (8%).** Among those, **two patients (2%)** also had an abnormal FLC ratio and an elevated IgG or IgA. These patients underwent a bone marrow biopsy and imaging and were **diagnosed with IgG-Kappa and IgA Kappa smoldering multiple myeloma (SMM)**, respectively. **The latter six patients (6%)** had a normal FLC ratio, and their characteristics were compatible with the **diagnosis of low risk MGUS**.
- Six of the eight patients with a detectable monoclonal protein were treated with a TKI (two patients were treated with imatinib, three patients with dasatinib, and one with bosutinib) and two were in treatment free remission (TFR).
- No differences in patients or disease characteristics were observed between patients with or without a paraprotein (Table I).
- When comparing different parameters at the time of paraprotein testing, we found:
 - **A trend towards higher rates of anemia in patients with a paraprotein (p=0.057).**
 - Similar rates of kidney failure, hypercalcemia, and similar levels of immunoglobulins, and gammaglobulin fraction on SPEP.
- **On univariate analysis** to assess for covariates for paraproteinemia occurrence:
 - Only the presence of anemia was predictive for paraproteinemia, albeit with borderline statistical significance (OR 5.118, CI 95% 0.978-26.790, p = 0.053).
 - Other parameters such as patients' characteristics (age, gender, other malignancies, vascular events), CML characteristics (risk categories, time since CML diagnosis, type of TKI) or other CRAB components (hypercalcemia or renal dysfunction) were not predictive for paraproteinemia.
- In the **multivariate analysis** model adjusted for age and gender, the existence of **anemia retained its predictive value**, again with borderline statistical significance (OR 4.751, CI 0.887-25.455 p= 0.069).

Table I – Cohort characteristics according to the existence of a paraprotein (n=100)

Characteristics	Patients without paraprotein (n=92)	Patients with paraprotein (n=8)	Total (n=100)
Gender, n (%)			
Male	44 (47.8)	6 (75)	50 (50)
Median age, year (range)			
At CML diagnosis	54.6 (23.9-90.4)	57.2 (39-68.5)	55.5 (23.9-90.4)
At enrollment & testing for a paraprotein	63.5 (26-91.6)	66.8 (46.2-74.2)	63.5 (26-91.6)
Median time from CML diagnosis, years (range)	6.1 (0.1-23.5)	12.2 (1.4-19.3)	6.3 (0.1-23.5)
CML characteristics at diagnosis			
Sokal score , number of patients with available data (%)	32	2	34
Low	18 (56.2)	0	18 (53)
Intermediate	12 (37.5)	1 (50)	13 (38.2)
High	2 (6.3)	1 (50)	3 (8.8)
Hasford score , number of patients with available data (%)	27	2	29
Low	16 (59.3)	1 (50)	17 (58.6)
Intermediate	7 (25.9)	1 (50)	8 (27.6)
High	4 (14.8)	0	4 (13.8)
Eutos score , number of patients with available data (%)	18	1	19
Low	17 (94.4)	1 (100)	18 (94.7)
Intermediate	1 (5.6)	0	1 (5.3)
High	0	0	0
CML therapy at time of enrollment & testing, n (%)			
1 st generation TKI	47 (51.1)	2 (25)	49 (49)
2 nd generation TKI	38 (41.3)	4 (50)	42 (42)
Patients in TFR	6 (6.5)	2 (25)	8 (8)
ABL001	1 (1.1)		1 (1)
Line of treatment (%)			
First line	58 (63)	4 (50)	62 (62)
Second line	23 (25)	1 (12.5)	24 (24)
Third line	8 (8.7)	3 (37.5)	11 (11)
Fourth line	3 (3.3)	0	3 (3)
CML Remission depth			
Median PCR level of bcr-abl1 (range)*	0.002 (0-11.3)	0 (0-0.96)	0.002 (0-11.3)

In all of the above characteristics, no statistically significant differences were observed between the two groups of patients, with and without a paraprotein.

CONCLUSIONS

- This is the **largest cross-sectional study** aiming to clarify the prevalence of paraproteinemia among CML patients.
- As a snapshot **we found the prevalence of MGUS in chronic phase CML patients (6%) to be higher than expected in the general population** above the age of 50 (3.2%) (1). **We also found a non-negligible prevalence of SMM (2%).**
- Based on these data and since MGUS and SMM may progress to active MM with end organ damage **we recommend considering screening for paraproteinemia coexistence in CML patients, especially in the presence of anemia.**
- Further studies and extended follow-up are needed to elucidate the true clinical significance of our findings.