

## Light Chain Multiple Myeloma: A Single Institution Series

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### Abstract

**Background:** Light chain multiple myeloma represents approximately 15% of myelomas and is considered a poor prognosis subtype. There are few series showing outcomes in real-life patients.

**Methods:** All consecutive symptomatic myeloma cases in our population-based registry from January 1993 to April 2015 have been included in this study. Clinical and laboratory characteristics have been compared in the light chain subtype with respect to other subtypes of myeloma. Overall survival has been analyzed in both groups.

**Results:** 63 patients (15.9%) had light chain myeloma in a series of 395 cases. Median overall survival was 21.1 months (8.9-33.3) in the light chain group versus 37.2 m (30.4-44.1) in other myeloma subtypes ( $p=0.014$ ).

**Conclusions:** Light chain multiple myeloma should be considered a subtype with poor prognosis, which is associated with several established negative prognostic factors such as stage ISS III, renal failure, male sex, high serum lactate dehydrogenase levels and high serum free light chain ratio.

**Keywords:** Multiple myeloma; Serum; Monoclonal gammopathies; Plasma cell leukemia

### Introduction

Multiple myeloma (MM) is a biologically complex and clinically heterogeneous disease [1] whose definition has been recently updated [2]. The prognosis of MM is currently based on the International Staging System (ISS) and the interphase fluorescence *in situ* hybridization (FISH) results [3]. However, many other prognostic factors may have a role in the outcome, including the subtype of MM. Symptomatic MM represents about 16.5% of the monoclonal gammopathies [4]. The subtype of MM characterized by the production of only lights chains (LCMM) can be found approximately in 15% of MM patients. The outcome of LCMM is considered worse than the other subtypes, but there are few studies that demonstrate this negative clinical impact. Here we report on a single institution population-based study with a series of 63 LCMM patients among 395 consecutive newly diagnosed MM (NDMM) patients.

### Patients and Methods

All NDMM patients who had their current residence at the time of diagnosis in Granada and met the diagnostic criteria of the International Myeloma Working Group [5], were included in the Granada population-based MM registry since 1993 and are the basis of this study, which was performed according to the Declaration of Helsinki (Ethics Committee approval number C-14, CEI-Gr, 2014). Patients with smoldering MM as well as plasma cell leukemia were excluded.

All common baseline prognostic factors were recorded, such as age, subtype of myeloma, Eastern Cooperative Oncology Group

(ECOG) performance status score, the presence of high-risk cytogenetic abnormalities by FISH including IgH translocations such as t(4;14) or t(14;16), del17p or abnormalities of chromosome 1, and ISS. Renal function was assessed by serum creatinine (sCr, mg/dL) and the estimated glomerular filtration rate (eGFR) according to the MDRD (modification of diet in renal disease) formula. Other variables of increasing interest were also included, such as the body mass index (BMI), the occurrence of weight loss before diagnosis, the delay in diagnosis (time from the first MM-related event to the bone marrow examination) as well as the therapeutic delay (time from bone marrow examination to date of initial treatment), the serum free light chain involved/uninvolved ratio (FLCr i/u), lactate dehydrogenase (LDH), C reactive protein, and the percentage of bone marrow plasma cell (BMPC) as measured by morphology.

Patients were treated with conventional chemotherapy until 2006, when we started to use a bortezomib-based induction approach. ASCT has been used since 1995.

Median overall survival (OS) was calculated in months (m) from the date of diagnosis (first bone marrow aspirate or biopsy) until

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the date of death, loss to follow-up, or end of study (April 24, 2015), whichever occurred first. The source of information for vital status of patients was the National Index of Deaths as well as the Andalusian Registry of Mortality. Comparisons for categorical variables among different groups were made with the  $\chi^2$ -test. Comparisons of means of quantitative continuous variables between two groups were made with the t-test. For multivariate analysis, key prognostic factors were introduced into a Cox proportional hazards model. All p-values were two-sided. No imputation for missing data has been used. Data were analyzed with SPSS v20 software.

## Results

Sixty-three patients (15.9%) had LCMM among the 395 patients included in our population-based registry. There were 38 males (60.3%). Median age was 64 years (21-87). The baseline clinical and laboratory characteristics of the LCMM group, in comparison with the other patients with MM, are shown in Table 1. Patients with LCMM had a significantly more advanced disease (according with ISS), a deeper renal impairment (according with sCr or eGFR), higher LDH levels and higher FLCr i/u. The disease presents a clear predominance for male sex and for the  $\lambda$ -FLC subtype. The BMI is also significantly lower in the LCMM. The other variables did not reach statistical significance. FISH data are available in only 70 patients but we did not find statistically significant differences for high risk abnormalities between LCMM and other subtypes. 68.5% of patients had a baseline eGFR <60 ml/min/1.73 m<sup>2</sup> and 33.3% < 15. In relation to sCr, 57.4% of patients had  $\geq 2$  mg/dL at the moment of diagnosis. Data of Cox multivariate OS model is shown in Table 2.

The treatment approach was similar in both groups. The percentage of patients undergoing autologous stem cell transplant (ASCT) was 25.4% in the LCMM and 28.6% in the other MM subtypes (p=0.377). First line therapy according to age and calendar period we summarized in Table 3.

Figure 1 show OS curves for the two groups. Median OS was 21.1 m (8.9-33.3) in the LCMM group versus 37.2 m (30.4-44.1) in other MM subtypes (p=0.014). According with the subtype of LCMM, median OS was 36.6 m (25.2-48) and 13.1 m (4.9-21.3) for  $\kappa$  and  $\lambda$ , respectively, but this difference did not reach statistical significance (p=0.514).

Even considering that most patients have some degree of baseline renal failure, the severity of the renal impairment has prognostic impact: OS in patients with sCr <2 or  $\geq 2$  was 37.3 m (7.2-67.4) and 8.9 m (0-20) respectively, p=0.092.

## Discussion

Patients with LCMM represent 15.9% of the MM in our series of 395 consecutive NDMM cases. This percentage is in accordance with previously reported data. Our data confirm that patients with LCMM have poorer outcome than other MM subtypes, in terms of OS. This worse prognosis is justified, to a certain point, by the association of LCMM with several established negative prognostic factors such as ISS III [6], renal failure [7], male sex [8], high LDH levels [9] and high FLCr i/u [10]. After adjustment for key prognostic factors, LCMM remains an independent factor associated with OS.

The highest baseline FLC levels have been previously associated

Clinical and laboratory characteristics	LCMM n: 63	Other MM subtype n: 332	p
Age (years)	64 (21-87)	67 (12-91)	0.198
Sex (% male)	60.3	47	<b>0.056</b>
Performance status by ECOG (% 3/4)	25.6 / 7	21.7 / 3.2	0.458
Weight loss (%)	29.5	27.6	0.706
Body Mass Index (Kg/m <sup>2</sup> )	26.9	28.4	<b>0.048</b>
Diagnostic delay (months)	7.52	5.82	0.205
Therapeutic delay (days)	22.7	45.3	0.239
International Staging System III (%)	73.3	43.3	<b>0.001</b>
Serum creatinine (mg/dL)	3.3	1.8	<b>&lt;0.001</b>
Glomerular filtration rate (ml/min/1.73 m <sup>2</sup> )	40.7	60.6	<b>&lt;0.001</b>
Lactate dehydrogenase (U/L)	421.3	282.6	<b>0.001</b>
C-reactive protein (mg/L)	4.04	3.36	0.656
Free Light Chain ratio (involved/uninvolved)	2152.6	333.9	<b>0.001</b>
Free Light Chain subtype (% Lambda)	57.1	37.4	<b>0.016</b>
Bone marrow plasma cell (%)	27.1	24.8	0.498
High risk cytogenetics by FISH (%)	27.3	22.4	0.496

Abbreviations: LCMM: Light Chain only MM, ECOG: Eastern Cooperative Oncology Group

**Table 1:** Baseline patient characteristics according to the subtype of MM.

Variables	HR	95% CI	p-value
Age	1.044	1.026-1.063	<0.001
ISS 2 (vs 1)	1.637	0.970-2.763	0.065
ISS 3 (vs 1)	2.335	1.386-3.934	0.001
LCMM (vs other subtype)	1.673	1.047-2.673	0.031
eGFR	0.995	0.988-1.002	0.158

Abbreviations: HR: Hazard Ratio, CI: Confidence Interval, ISS:International Staging System, LCMM: Light Chain only MM, eGFR: estimated Glomerular Filtration Rate (ml/min/1.73 m<sup>2</sup>).

**Table 2:** Cox multivariate model for survival.

	Age < 65 years				Age ≥ 65 years			
	1995-99	2000-04	2005-09	2010-14	1995-99	2000-04	2005-09	2010-14
MP, n.(%)	10(47.6)	1(2.2)	0	1(1.6)	18(75)	33(64.7)	27(46.6)	4(6.2)
VAD	11(52.4)	40(88.9)	33(78.6)	3(4.8)	3(12.5)	13(25.5)	18(31)	0
VCMP/VBAP	0	3(6.7)	2(4.8)	0	0	2(3.9)	0	0
VD	0	0	4(9.5)	19(30.6)	0	0	1(1.7)	9(13.8)
VMP	0	0	2(4.8)	1(1.6)	0	0	8(13.8)	33(50.8)
VCD	0	0	0	20(32.3)	0	0	0	7(10.8)
VRD	0	0	0	13(21)	0	0	0	0
OTHER	0	1(2.2)	1(2.4)	5(8.1)	3(12.5)	3(5.9)	4(6.9)	12(18.5)
SCT1, n	11	30	28	36	1	4	1	0
SCT2, n	2	10	2	6	0	0	0	0

Abbreviations: SCT: Stem Cell Transplant; MP: Melphalan-Prednisone; VAD: Vincristine-Doxorubicin-Dexamethasone; VCMP/VBAD: Vincristine-Cyclophosphamide-Melphalan-Prednisone / Vincristine-Carmustine(BCNU)-Doxorubicin-Prednisone; VD: Bortezomib-Dexamethasone; VMP: Bortezomib-Melphalan-Prednisone; VCD: Bortezomib-Cyclophosphamide-Dexamethasone; VRD: Bortezomib-Lenalidomide-Dexamethasone; OTHER: other Bortezomib-based combinations

Table 3: Induction therapy and SCT according to age and calendar period.

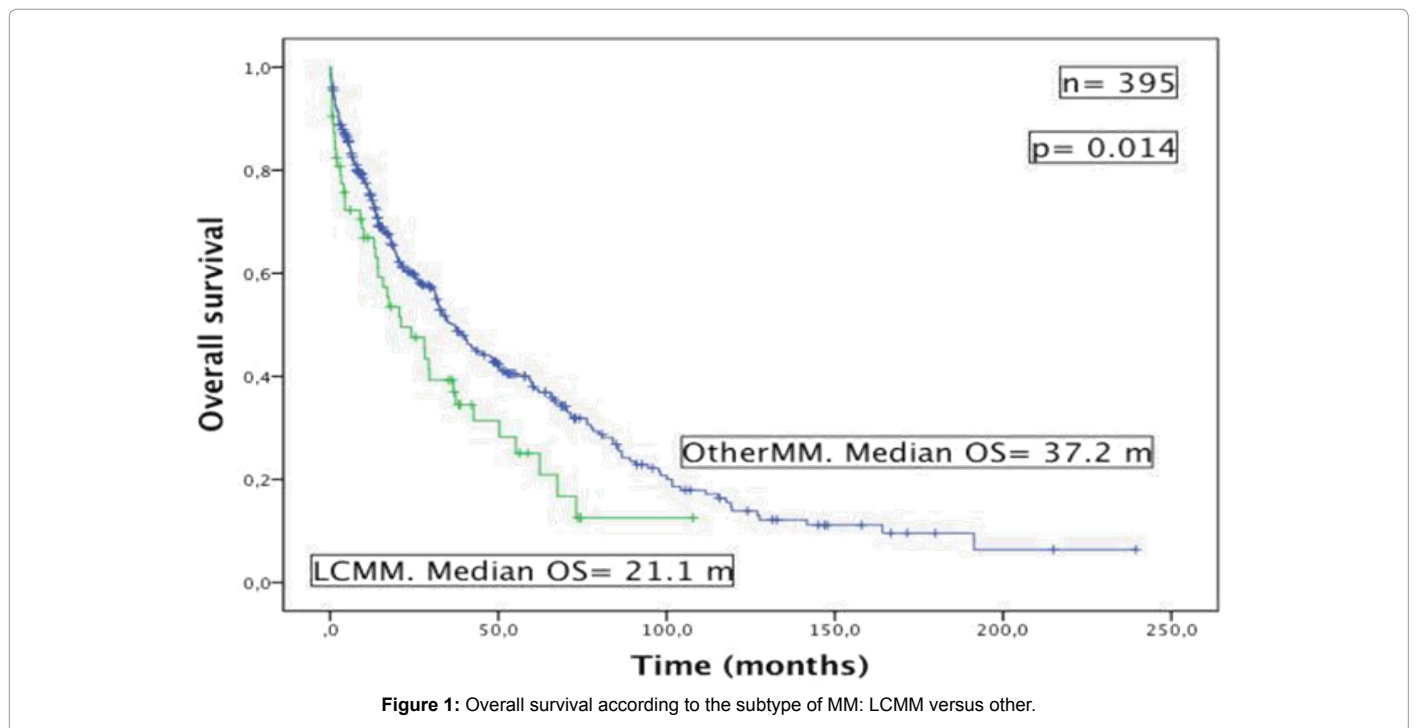


Figure 1: Overall survival according to the subtype of MM: LCMM versus other.

with LCMM [11]. Consensus guidelines have been reported for the use of FLC assay [12].

There are few studies about outcome of real-life LCMM patients in the era of the novel agents, but Zhang et al. [13] have recently reported 96 LCMM patients in a series of 459 cases, highlighting that this subtype of MM have a more aggressive disease and poor outcome. 60.4% of the cases had ISS III stage and 33.3% extramedullary disease. Median age was 58 years (28-86). Median OS was 23 m (4-67) in the bortezomib treated group and 12 m (4-67) in the group without bortezomib, respectively. This study does not report data about FLCr i/u, FISH or other clinical variables such as the percentage of patients undergoing ASCT.

LCMM should be considered a subtype of MM with poor prognosis. Every effort should be made to improve OS in this subtype of MM, in particular in those with severe renal failure. Patients with reversal of

renal impairment have improved outcomes, but it remains inferior to patients with normal renal function at diagnosis [14]. Early application of high cut-off haemodialysis as well as an optimized use of novel agents [15] can help to reverse renal failure. Furthermore, diagnosis should be made as soon as possible to avoid irreversible renal damage.

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