HOSPITAL UNIVERSITARIO DE SALAMANCA

IBSAL Instituto de Investigación Biomédica de Salamanca

University of Salamanca

Should we treat Smoldering Myeloma?

María-Victoria Mateos
University Hospital of Salamanca- IBSAL
Salamanca. Spain

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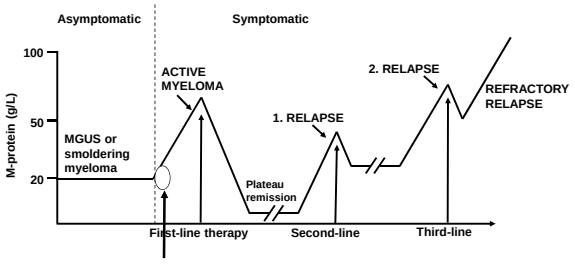
Yes…....
But I am going to try to explain why?

María-Victoria Mateos
University Hospital of Salamanca- IBSAL
Salamanca. Spain

Natural History of Multiple Myeloma



What does active Myeloma mean?

MGUS=monoclonal gammopathy of undetermined significance.

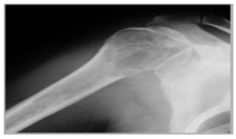
Signs and Symtoms

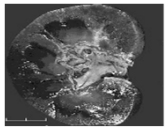
What are the signs and symptoms of Multiple myeloma?

- Bone pain, usually in the back and ribs

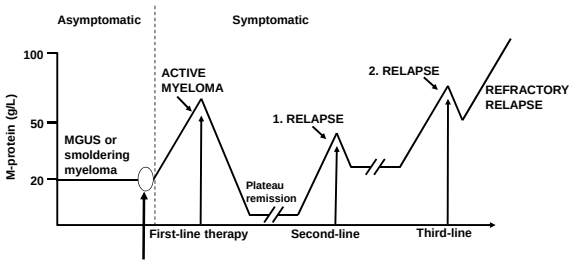
- Broken bones, usually in the spine

- Frequent infections and fevers





Natural History of Multiple Myeloma



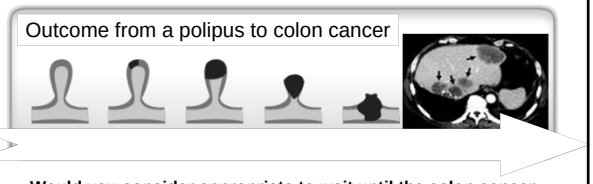
Does this make sense?
Is this something ridiculous?

MGUS=monoclonal gammopathy of undetermined significance.

Non-hematologic malignancies: Oncology perspective

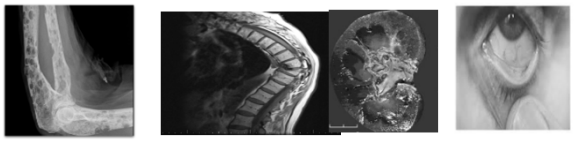
Early intervention

- **In almost all malignancies (breast, prostate, colon cancers,...)**
- **Two possible objectives: To cure/erradication**
  To delay progression to active disease



Would you consider appropriate to wait until the colon cancer resulted in liver involvement to plan active treatment?

- This is what Dr Leleu proposes for patients with SMM
- He will propose to wait until myeloma-related symptomatology is developed



And although I don't agree with him.....

- I tried to put in Dr Leleu's mind to understand his thoughts

Is there any rationale ?

Smouldering Multiple Myeloma: Management

Agents	ORR (%)	TTP	OS	Reference
Early MP* vs Deferred MP	52 vs 55	No benefit	No benefit	Hjorth M, et al. Eur J Haematol. 1993 Grignani G, et al. Br J Cancer. 1996 Riccardi A, et al. Br J Cancer. 2000
Thal+Zol vs Zol**	37 vs 0	No benefit	No benefit	Witzig TE, et al. Leukemia 2013
Bisphosphonates***vs observation	0	No benefit	No benefit	Martin A, et al. Br J Haematol. 2002 D'arena et al. Leuk Lymphoma. 2011 Musto P, et al. Cancer. 2008

**Abandon: No differences in survival and potential risk of secondary leukemias*

***Low efficacy&high rates of discontinuation due to PN*

****Skeletal related events lower in the bisphosphonate groups **(39% vs 73% and 55% vs 78%)***

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Low, intermediate and high risk patients were included

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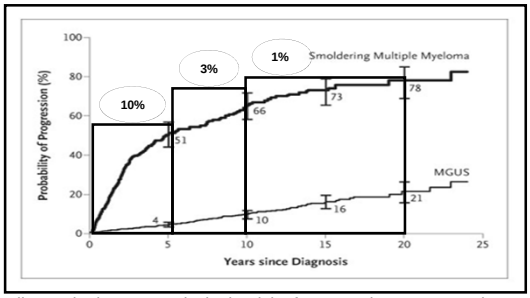
Smouldering Multiple Myeloma: Risk of progression to active disease



According to the heterogeneity in the risk of progression to MM, we have to identify the individual risk for each new SMM patient.

Is it possible to identify the risk of progression? Is it easy to doing this?

Kyle R. N Engl J Med 2007; 356:2582-90

Identification of the risk of progression to MM

- **Mayo Clinic model**
- **Spanish model**
- **Bence-Jones proteinuria**
- **Cytogenetic abnormalities**
- **Gene-expression profiling**
- **PET-CT**
- **Pattern of evolution of M-spike**
- **…….**

All of them are able to identify a subgroup of patients with a 50% risk of progression at 2 years

How to proceed in the clinic with these different risk models?

- **There is a IMF proposal to build an International Staging System for SMM to define the risk of progression to Myeloma in an homogeneous way (available next year)**

How to proceed in the mean time?

- My proposal is to use:
  - **Mayo Clinic model**→available in all centers
  - **Spanish model**→if flow is available
  - **Evolving pattern**→dynamic, easy and predictive along the course of the disease

Is it possible to do this?

Is there any concordance between the different risk models?

Disagreement between smoldering myeloma risk models

Distribution of 77 SMM patients using both the Mayo and Spanish models. Overall agreement 22/77 (28.6%)

	PETHEMA low, n	PETHEMA mid, n	PETHEMA high, n
Mayo low, n	11	15	12
Mayo mid, n	6	7	22
Mayo high, n	0	0	4

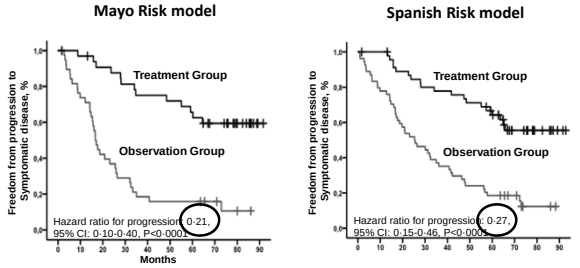
Significant disagreement between models (p<0.0001)

- **Do you know what the real outcome of these patients with disagreement was?**
- **Were actually they at low, intermediate or high risk?**
- **Nobody knows**

Cherry et al. *Leuk Lymphoma 2013*

Concordance between Mayo and Spanish model

Len-dex vs no treatment: TTP to active disease (n = 119)



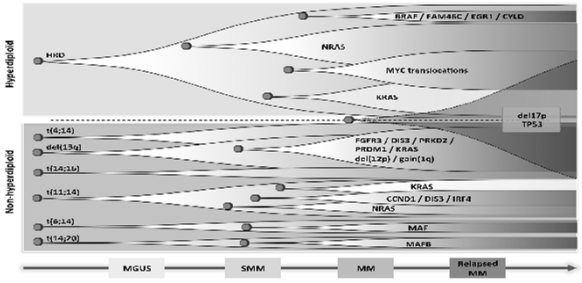
Both risk models resulted as independent prognostic factors in multivariate analysis including large number of patients with long f/u

Mateos MV et al. Lancet Oncology 2016

Is there any additional reason to plan early treatment?
Any biological reason?

Model for molecular pathogenesis of SMM and MM

Large-scale whole-exome sequencing studies have provided new insights into the clonal heterogeneity and evolution of the disease. According to the primary genetic events involved in tumorigenesis, MM tumours are hierarchically subdivided into hyperdiploid and non-hyperdiploid subtypes; subsequently, secondary genetic events lead to tumour progression.



Manier, Salom, et al. *Nat Rev Clin Oncol*, 2016

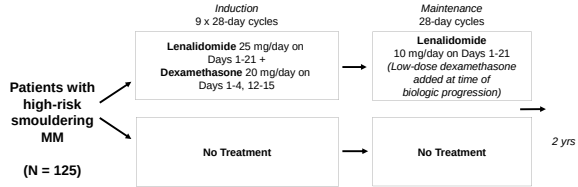
Should we treat every patient with high risk smoldering Myeloma?

- **Smoldering Myeloma is a heterogeneous disease**
- **It is possible to identify the high risk subgroup of SMM patients**
- **The oncologic perspective supports the early treatment**
- **The biology of the disease is different,…..**

I would plan early treatment for every high risk SMM

QuiRedex: Study Design

- Multicenter, open-label, randomized phase III trial



In both arms, blood counts, biochemical analysis (including creatinine and calcium) and serum/urine levels of MC were performed monthly. Skeletal survey was performed during the screening phase and thereafter only if clinical symptoms emerged.

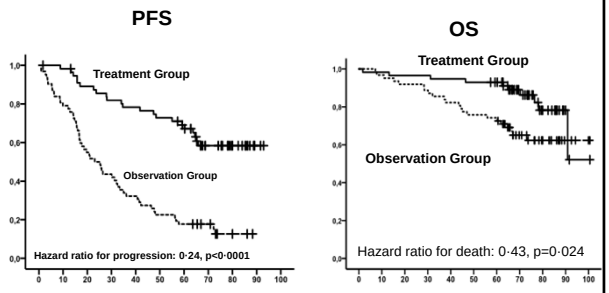
High-risk was defined according to the Mayo and/or Spanish models

Mateos MV, et al. NEJM 2013; 369:438-47

Len-dex vs no treatment: TTP to active disease (n = 119)

Per-protocol Patients population

Median follow-up: 75 m



Mateos MV, et al. NEJM 2013

Mateos MV, et al. Lancet Oncology 2016

QuiRedex: toxicity profile during induction (n:125)

	Len-dex arm (n:62)		Abstention arm (n:63)
	G1	G2	G1-2
Anemia	11 (20%)	4 (7%)	2 (4%)
Neutropenia	3 (6%)	8 (14%)	
Thrombopenia	6 (11%)	1 (2%)	
Asthenia	6 (11%)	5 (9%)	6 (11%)
Constipation	4 (7%)	6 (11%)	1 (2%)
Diarrhea	9 (17%)	4 (7%)	2 (4%)
Rash	12 (23%)	6 (11%)	
Infection*	19 (35%)	6 (11%)	14 (26%)
DVT**	1 (2%)	2 (4%)	
SPM -Hematologic -Non hematolog	1 patient (PV) 5 patients*		1 patient (MDS)

*3 prostate cancers, 1 breast cancer and 1 cervical epidermoid carcinoma

The cumulative risk of developing a second primary malignancy at 7 years was 12% 0.31–11) in the treatment group and 3% in the observation group (p=0.070).

The exposure was not symmetric: 342 pts-years in Len-dex vs 70 pts-years in the control arm

Mateos MV, et al. Lancet Oncology 2016: accepted for publication

Should we treat every patient with high risk smoldering Myeloma?

- **Smoldering Myeloma is a heterogeneous disease**
- **It is possible to identify the high risk subgroup of SMM patients**
- **The oncologic perspective supports the early treatment**
- **The biology of the disease is different,…..**
- **Early treatment delays the progression to MM and prolongs the OS**

This study was the starting point to plan early treatment in SMM

This was the rationale for new definition of MM

mvm

Panel: Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

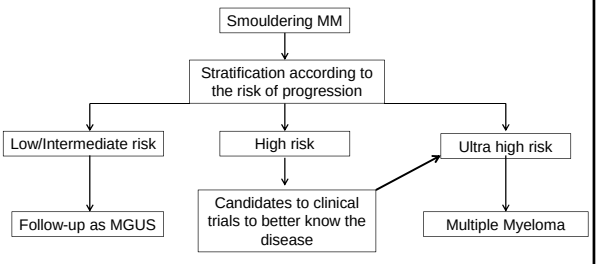
- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage* ≥60%
  - Involved:uninvolved serum free light chain ratio§ ≥100
  - >1 focal lesions on MRI studies¶

Some patients called SMM some years ago are now MM and we treat them as active MM

‡ If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
¶ Each focal lesion must be 5 mm or more in size.

Rajkumar et al. Lancet Oncology 2014; 15: e538-48

What was the near future?



Current studies in High-risk Smouldering Multiple Myeloma

- **Numerous clinical trials (51 in clinicaltrials.gov) with several drugs are currently ongoing in this group of patients**
- **To delay the disease progression**
  - **Elo-Rd, Daratumumab, KRd, Ixazomib-Rd, pembrolizumab, nivolumab-Rd, isatuximab,…**
- **To cure the disease**
  - **CESAR trial**
  - **ASCENT trial**

Phase 2 study with Carfilzomib-Rd x 8c→Rd in high risk Smoldering MM (n=12)

Best treatment response	High-risk smoldering myeloma (%) (N = 12)	Newly diagnosed multiple myeloma (%) (N = 45)
Complete response	12 (100)	25 (56)
EuroFlow (MRD 10^{-5} negative)	11/12 (92)	33/43 (77)
Next Gen VDJ Sequencing (MRD 10^{-6} negative)	9/12 (75)	14/33 (42)

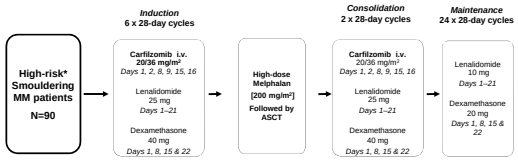
Adapted from Korde et al.[14]

Patients with high-risk SMM responded better than active MM because we are treating a different disease from the biological point of view

Landgren O et al. ASH 2017:Educational session

GEM-CESAR: Study Design

- Multicenter, open-label, phase II trial



High-risk was defined according to the Mayo and/or Spanish models

- Patients with any one or more of the biomarkers predicting imminent risk of progression to MM were allowed to be included but…
- New imaging assessments were mandatory at screening and if bone disease was detected by CT or PET-CT, patients were excluded

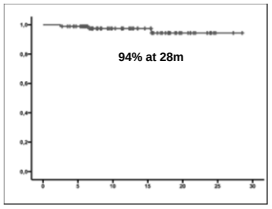
GEM-CESAR (n=90)

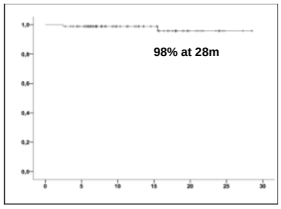
Response category	Induction (n=71)	HDT-ASCT (n=42)	Consolidation (n=35)	Maintenance (n=29)
ORR	**69 (98%)**	**42 (100%)**	**35 (100%)**	**29 (100%)**
sCR	21 (**30%**)	22 (**52%**)	24 (**69%**)	24 (**83%**)
CR	9 (**13%**)	2 (**5%**)	2 (**6%**)	2 (**7%**)
VGPR	27 (38%)	12 (29%)	7 (20%)	2 (7%)
PR	12 (17%)	6 (14%)	2 (6%)	1 (3%)
SD				
MRD –ve,	31%	50%	60%	N/A
Relapse from CR	2 (3%)	-	-	-
Clinical progression	-	-	-	-

Toxicity profile: *** Induction: 3 and 5% of G3-4 neutropenia & thrombocytopenia, respectively; 2 pts had G3-4 pneumoniae; 1 pt G3 cardiac failure; 2 pts G2 hypertension.**
*** Transplant: All but one collected PBSC and all engrafted**
*** No major toxicities reported during consolidation and maintenance**

GEM-CESAR Outcomes

PFS Median follow-up: 10 (1-28) **OS**

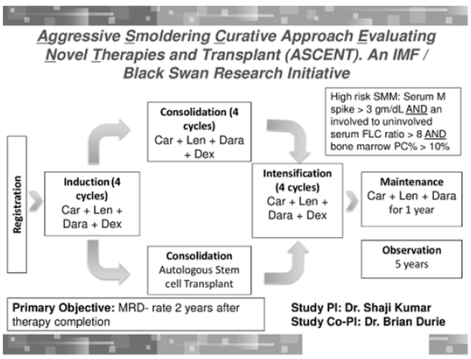




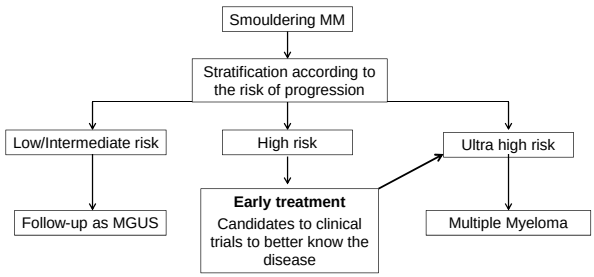
Two patients experienced relapse from CR before the end of induction and they proceeded to subsequent therapy

Two deaths: one patient who relapsed from CR and was refractory and died due to disease progression; other patient due to massive ischemic stroke during induction

Aggressive Smoldering Curative Approach Evaluating Novel Therapies and Transplant (ASCENT)



SMM: What will be the future?



In the near future, we will treat to high risk SMM patients, especially because new biomarkers will be validated and more SMM patients will be considered as Myeloma and patients will be treated as patients with active disease

Acknowledgments

- **All investigators including patients in our clinical trials and most of all, thanks to the patients and families**