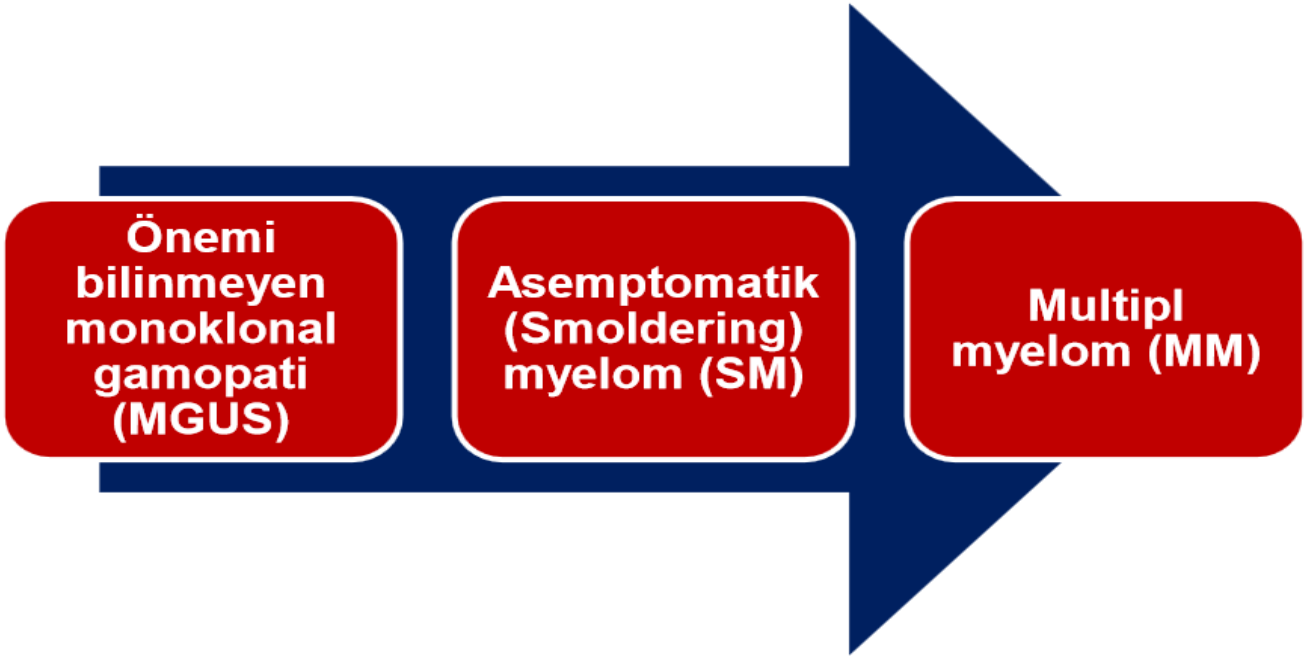
Yeni kriterler eşliğinde smoldering multipl myelom Tedavi edelim mi?

Doç Dr Tuba Hacıbekiroğlu

Eylül 2016


Önemi bilinmeyen monoklonal gamopati (MGUS)
Asemptomatik (Smoldering) myelom (SM)
Multipl myelom (MM)

* SMM insidansı : 100.000 / 0,44
* Multipl myelom tanısı almış hastaların % 14 ‘ü SMM
* Ortalama yaş benzer olarak 65-70

Kristinsson SY, HolmbergE,BlimarkC.Treatmentforhigh-risksmolderingmyeloma.NEnglJMed.2013;369:1762-1763.

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Merlini, María-Victoria Mateos, Shaji Kumar, Jens Hillengass, Efstathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Sonja Zweegman, Sagar Lonial, Laura Rosinol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan José Lahuerta, Hans Erik Johnsen, Meral Beksac, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel

Lancet Oncol 2014; 15: e538–48

This International Myeloma Working Group consensus updates the disease definition of multiple myeloma to include validated biomarkers in addition to existing requirements of attributable CRAB features (hypercalcaemia, renal failure, anaemia, and bone lesions). These changes are based on the identification of biomarkers associated with near inevitable development of CRAB features in patients who would otherwise be regarded as having smouldering multiple myelom… be detrimental to t… and radiographic var… ical and monoclonal… new biomarkers sho… oup recommends the… nds that future studi…

- KEMİK İLİĞİ PLAZMA HÜCRESİ> %60
- FLR > 100
- 2 VE ÜZERİ KEMİK LEZYONU = **ULTRA HİGH RİSK**

= %80 – 90 HASTA 2 YIL İÇİNDE SEMPTOMATİK MYELOM OLACAK !!!

= BU HASTALAR ARTIK MULTİPL MYELOM !!!

Introduction

Multiple myelo… the clonal plasma c… nc- always preceded… ent. termed monoc… ally significance (M… of a 3–4% of the pop… (ie., diagnosis of M… ncy calcaemia, rena… r to (referred to as C… as the underlying plasma cell disorder (all features must be absent; table 1).[1–10] About 80% of multiple myeloma originates from non-IgM immunoglobulin MGUS (non-IgM MGUS), and 20% from light-chain immunoglobulin

organ damage within the first 2 years of diagnosis.[11,12] Unfortunately, no single pathological or molecular feature can be used to distinguish patients with smouldering multiple myeloma who have only clonal

See Online for a podcast interview with S Vincent Rajkumar

Division of Hematology, Mayo Clinic, Rochester, MN, USA (Prof S V Rajkumar MD, Prof S Kumar MD, Prof A Dispenzieri MD, Prof R A Kyle MD); Department of Clinical Therapeutics, University of Athens, School of Medicine, Athens, Greece (Prof M A Dimopoulos MD, E Kastritis MD, E Terpos MD); Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy (Prof A Palumbo MD); Hospital Clinic, Barcelona, Spain (J Blade MD, L Rosinol MD); Amyloidosis Center, University Hospital Policlinico San Matteo, Pavia, Italy (Prof G Merlini MD); University Hospital of Salamanca/IBSAL, Salamanca, Spain (M V Mateos MD); Department of Hematology, Oncology and

ULTRA HİGH RİSK

* Tüm vücud MRI da birden fazla kemik lezyonunda TTP 13 ay (*Hillengass J, Fechtner K, Weber MA, et al. Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma.JClinOncol.2010;28:1606-1610.)*
* Kemik iliği plazma hücresi> %60 olan hastalarda TTP 7,7 ay ve %95 2 yıl içinde semptomatik myelom gelişiyor. (*Rajkumar SV, Larson D, Kyle RA. Diagnosis of smoldering multiple myeloma.NEnglJMed.2011;365:474-475.)*
* *FLR> 100 hastalarda TTP 18 ay*
  (KastritisE,TerposE,MoulopoulosL,etal.Extensivebonemarrowinfiltration and abnormal free light chain ratio identifies patients with asymptomatic myeloma at high risk for progression to symptomatic disease.Leukemia.2013;27:947-953.

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

Definition of multiple myelo

Clonal bone marrow plasma
plasmacytoma* and any one

- Myeloma defining events
  - Evidence of end organ proliferative disorder,
    - Hypercalcaemia: s upper limit of nor
    - Renal insufficiency >177 μmol/L (>2 n
    - Anaemia: haemog haemoglobin valu
    - Bone lesions: one PET-CT‡
  - Any one or more of th
    - Clonal bone marro
    - Involved:uninvolv
    - >1 focal lesions on

Definition of smouldering mu

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis

PET-CT=^{18}F-fluorodeoxyglucose PET with CT. *Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. †Measured or estimated by validated equations. ‡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. §These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ¶Each focal lesion must be 5 mm or more in size.

Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis

PET-CT=^{18}F-fluorodeoxyglucose PET with CT. *Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. †Measured or estimated by validated equations. ‡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. §These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ¶Each focal lesion must be 5 mm or more in size.

myeloma diagnosed at the Mayo Clinic between January, 1996, and June, 2010.[45] Only 21 (3%) patients had a BMPC of 60% or greater, and 95% of these

(5%) of 121 patients with smouldering multiple myeloma in a third study were reported to have BMPC

myeloma, and more than 90% of patients with multiple myeloma have altered FLC ratios that indicate excess production of a clonal FLC by the proliferating plasma cell population.[27,44,65,66] The presence of an abnormal FLC ratio, and the extent to which the FLC ratio is abnormal, predict risk of progression in MGUS, smouldering multiple myeloma, amyloid light-chain (AL) amyloidosis, and solitary plasmacytoma.[27,44,67]

Dispenzieri and colleagues[44] reported that in patients with smouldering multiple myeloma, an involved to uninvolved FLC ratio of 8 or more is associated with about a 40% risk of progression within the first 2 years from diagnosis. Subsequently, Larsen and colleagues[68] studied 586 patients with smouldering multiple myeloma to determine the threshold at which the FLC ratio is

1-Organ Hasarı Kanıtları: Ca> 11 mg/dl, Hb< 10 gr/dl, kreatin> 2 mg/dl, GFR< 40 ml/dk, ≥ 1 litik lezyon

2- Kanser Biyomarkırları: Kemik iliği plazma hücresi> %60, free light chain (FLC) oranı ≥ 100, MRI da > 1 fokal lezyon

* Smolderin Myel
* ➡ Ig G veya Ig
  Bence Jones Pr 500 mg / 24 h
* Ve/ veya ➡ Kemik ili ma hücresi %10-60

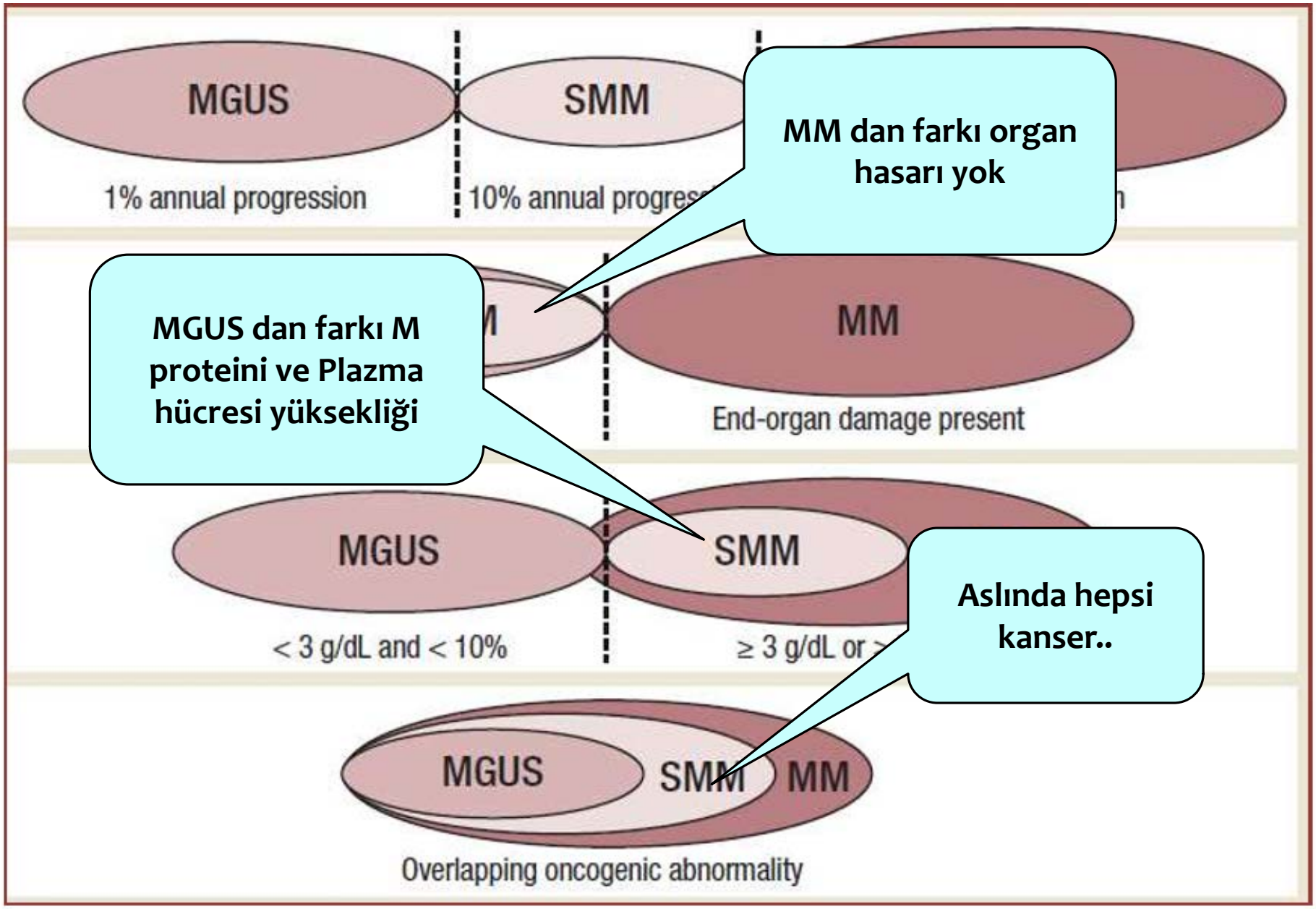
+

* VE ➡ Myelom ilişkili olayların (myeloma defınıng events MDE) veya amiloidozun olmaması

TABLE 1. Differential Diagnosis of MGUS, SMM, and Symptomatic MM

Feature	MGUS	SMM	MM
Serum-M protein	< 3 g/dL and	≥ 3 g/dL and/or	
Clonal BMPC infiltration	< 10%	10-60%	≥ 10% or biopsy-proven plasmacytoma
Symptomatology	Absence of CRAB*	Absence of MDE** or amyloidosis	Presence of MDE**

Abbreviations: MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; MM, multiple myeloma; BMPC, bone marrow plasma cell; CRAB, hypercalcemia, renal failure, anemia, and bone; MDE, myeloma-defining event.
*CRAB includes (1) hypercalcemia: serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL); (2) renal insufficiency: serum creatinine > 177 μmol/L (2 mg/dL) or creatinine clearance < 40 mL/minute; (3) anemia: hemoglobin value of > 2 g/dL below the lower normal limit, or a hemoglobin value < 10 g/dL; (4) bone lesions: one or more osteolytic lesion revealed by skeletal radiography, CT, or PET-CT.
**MDE: Myeloma-defining events include CRAB symptoms (above) or 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 revealed by MRI studies.



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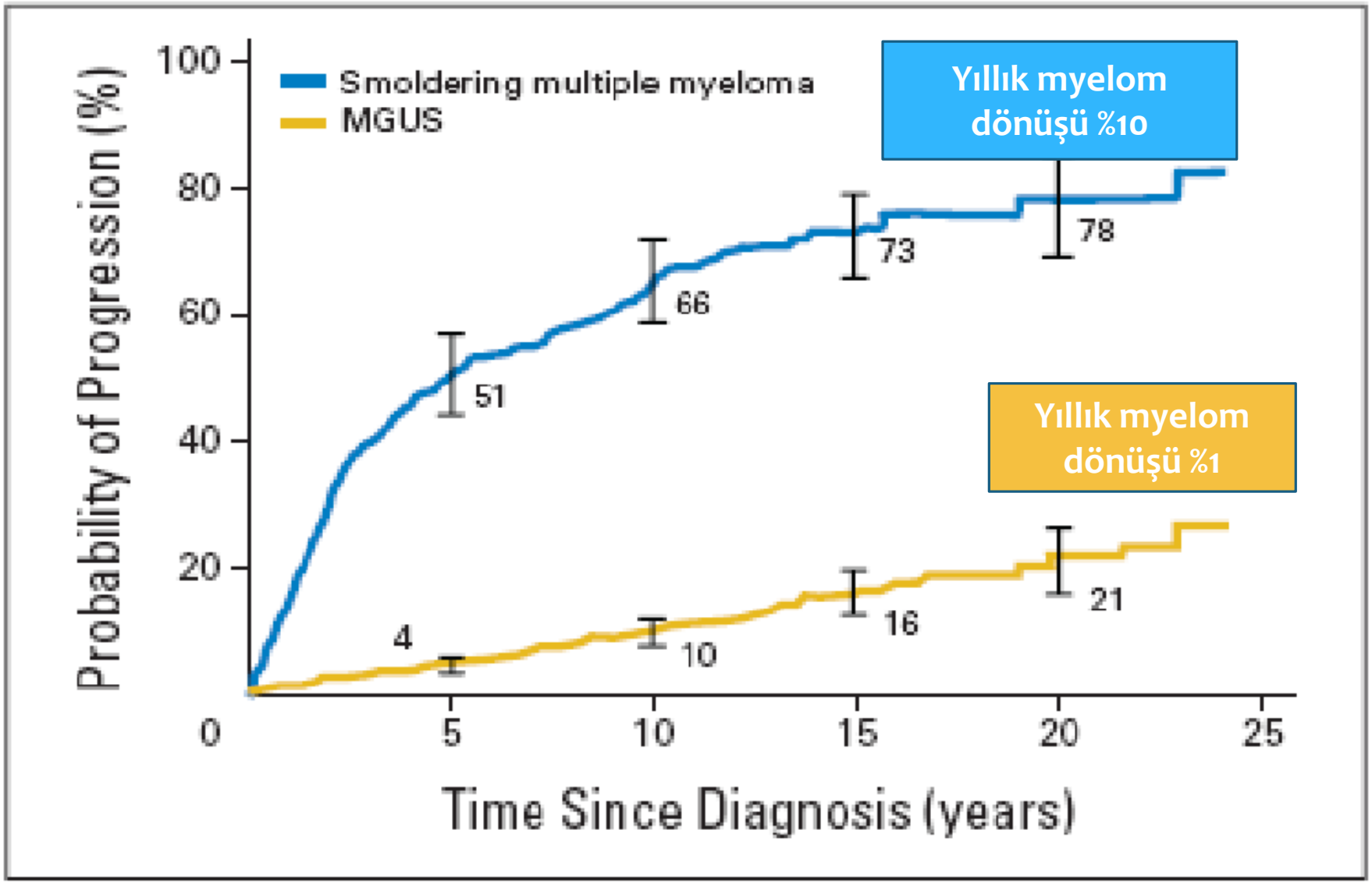

JCO 2010;28(4):690-696

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clinical Course and Prognosis of Smoldering (Asymptomatic) Multiple Myeloma

Robert A. Kyle, M.D., Ellen D. Remstein, M.D., Terry M. Therneau, Ph.D., Angela Dispenzieri, M.D., Paul J. Kurtin, M.D., Janice M. Hodnefield, M.S., Dirk R. Larson, M.S., Matthew F. Plevak, B.S., Diane F. Jelinek, Ph.D., Rafael Fonseca, M.D., Lee Joseph Melton III, M.D., and S. Vincent Rajkumar, M.D.

From the Division of Hematology (R.A.K., A.D., R.F., S.V.R.), the Department of Laboratory Medicine and Pathology (E.D.R., P.J.K., J.M.H.), the Division of Biostatistics (T.M.T., D.R.L., M.F.P.), the Department of Immunology (D.F.J.), and the Department of Health Sciences Research (L.J.M.), Mayo Clinic, Rochester, MN. Address reprint requests to Dr. Kyle at the Division of Hematology, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, or at kyle.robert@mayo.edu.

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

ABSTRACT

BACKGROUND

Smoldering (asymptomatic) multiple myeloma is an asymptomatic plasma-cell proliferative disorder associated with a high risk of progression to symptomatic multiple myeloma or amyloidosis. Prognostic factors for the progression and outcome of this disease are unclear.

METHODS

We searched a computerized database and reviewed the medical records of all patients at Mayo Clinic who fulfilled the criteria of the International Myeloma Working Group for the diagnosis of smoldering multiple myeloma between 1970 and 1995. Bone marrow aspirate and biopsy specimens were studied, and patients were followed throughout the course of disease.

RESULTS

During the 26-year period, 276 patients fulfilled the criteria for smoldering multiple myeloma. During 2131 cumulative person-years of follow-up, symptomatic multiple myeloma or amyloidosis developed in 163 persons (59%). The overall risk of progression was 10% per year for the first 5 years, approximately 3% per year for the next 5 years, and 1% per year for the last 10 years; the cumulative probability of progression was 73% at 15 years. At diagnosis, significant risk factors for progression included the serum level and type of monoclonal protein, the presence of urinary light chain, the extent and pattern of bone marrow involvement, and the reduction in uninvolved immunoglobulins. The proportion of plasma cells in the bone marrow and the serum monoclonal protein level were combined to create a risk-stratification model with three

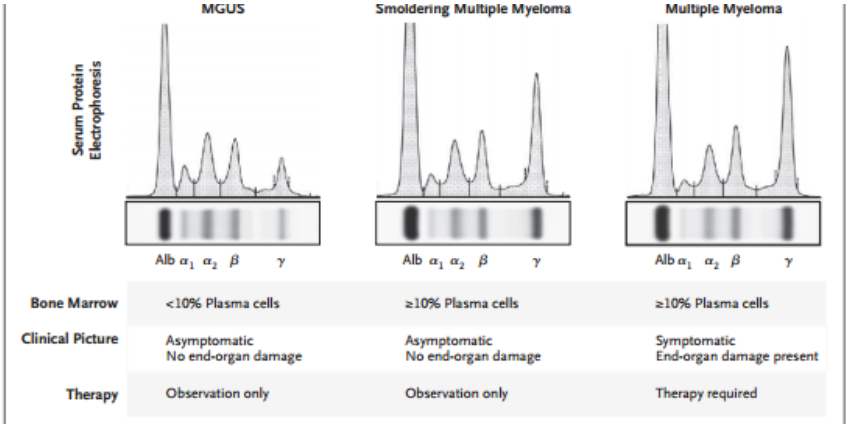

Figure 4. Characteristics of Active Multiple Myeloma and Its Precursors.

Monoclonal gammopathy of undetermined signi
tomatic precursors of active multiple myelom
prominent monoclonal protein in the γ regio
features that can be used to distinguish these
cemia, anemia, renal failure, or lytic bone les

tiple myeloma have been affected by th
ity in the criteria used to establish the dia
Inconsistent diagnostic criteria in previ
ies have resulted in the reporting of var
dian times to progression.[1-7] Our study s
the risk of progression is significantly a
the level of monoclonal protein, the prop
bone marrow plasma cells, or both. There
also substantial differences in the median time to
progression among the three risk groups (2, 8, an
19 years).

Our study shows that the overall risk of
gression in smoldering multiple myeloma i
ly influenced by the time elapsed since d osis,
in contrast to the risk of progression i MGUS,[19]
which remains constant over time. We found that
the overall risk of progression among patients with
smoldering multiple myeloma was approximately
10% per year in the first 5 years and 3% per year
in the next 5 years with a decrease to 1% per year
thereafter. No such time-dependent change in risk
occurs with MGUS.[19]

Other investigators have reported that the IgA
isotype and the presence of urinary monoclonal
protein are adverse prognostic factors for patients

ution of heavy-chain and light-chain
similar to those in patients with active
ple myeloma.[21] However, other findings, such
a reduction in the level of uninvolved immuno-
globulins[19,21] and the presence of monoclonal
urinary light chains, were intermediate between
those in patients with active multiple myeloma and
those in patients with MGUS.

On the basis of our experience, we suggest that
the standard of care for patients with smoldering
multiple myeloma should be close follow-up every
few months. Physicians should repeat the perti-
nent laboratory tests 2 to 3 months after the initial
recognition of the disease to rule out an early
active form; if the results are stable, the studies
should initially be repeated every 4 to 6 months.
However, given the high risk of progression among

We found that the overall risk of progression among patients with smoldering multiple myeloma was approximately 10% per year in the first 5 years and 3% per year in the next 5 years with a decrease to 1% per year thereafter.

BAŞLANGIÇ DEĞERLENDİRME

SIDEBAR 1. Evaluation of Patients Newly Diagnosed With SMM

- Medical history and physical examination
- Hemogram
- Biochemical studies, including of creatinine and calcium levels; beta 2-microglobulin, LDH, and albumin
- Protein studies
  - Total serum protein and serum electrophoresis (serum M-protein)
  - 24-hour urine sample protein electrophoresis (urine M-protein)
  - Serum and urine immunofixation
- Serum free light-chain measurement (FLC ratio)
- Bone marrow aspirate with or without biopsy: infiltration by clonal plasma cells, flow cytometry, and fluorescence in situ hybridization analysis
- Skeletal survey, CT, or PET-CT
- MRI of thoracic and lumbar spine and pelvis; ideally whole-body MRI

Abbreviations: SMM, smoldering multiple myeloma; LDH, lactate dehydrogenase; PET-CT, ^{18}F-fluorodeoxyglucose (FDG) PET/CT.

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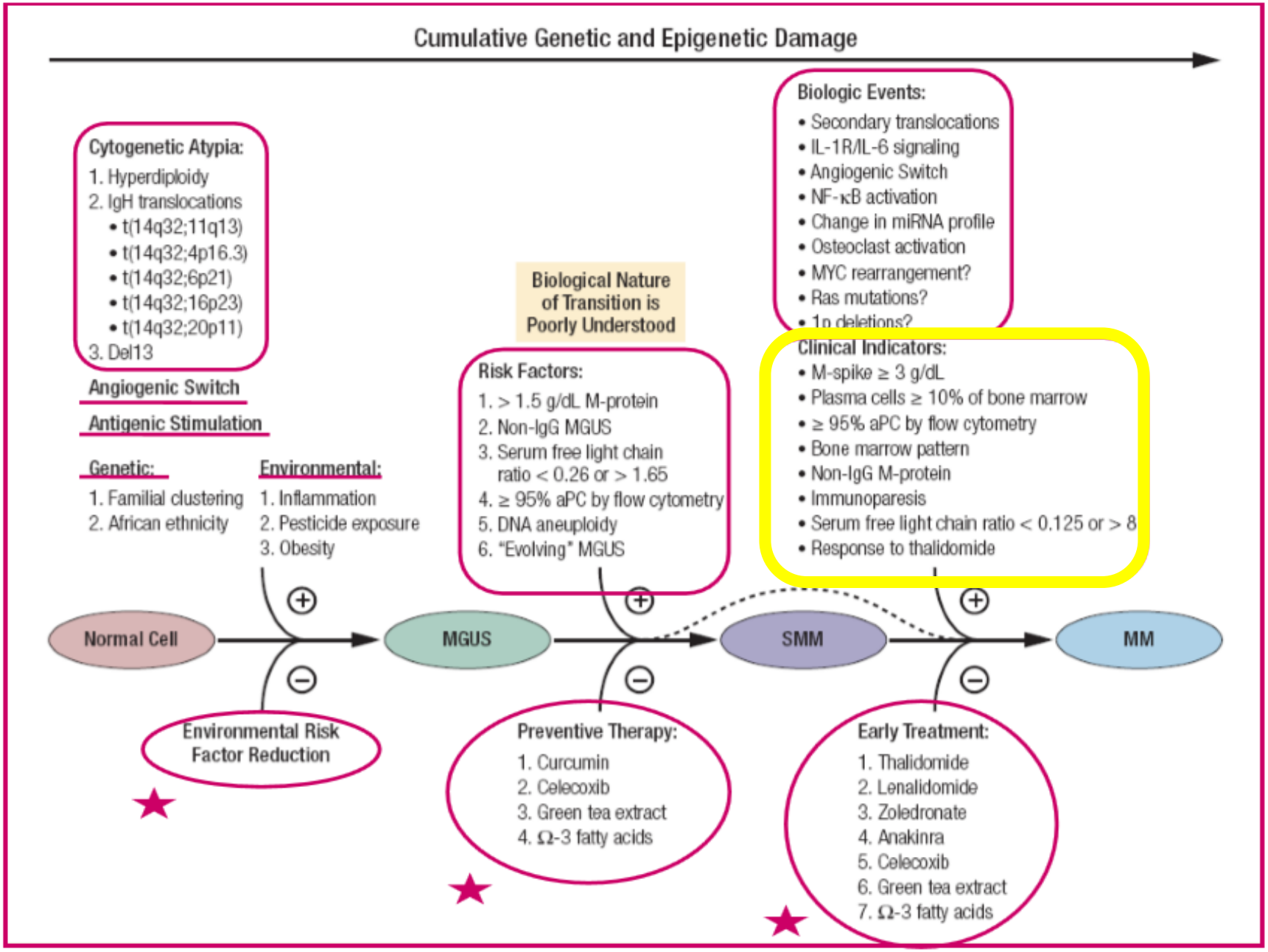
Asemptomatik / Smoldering Myelom

Sem Hematol 2011;48(1):66-72



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SIDEBAR 2. Smoldering MM: Markers Predicting Progression to Symptomatic MM

Features for Identifying High-Risk SMM: 50% at 2 Years

- **Tumor Burden**
  - ≥ 10% clonal plasma cell bone marrow infiltration plus
  - ≥ 3 g/dL of serum M-protein and
  - Serum free light-chain ratio of 0.125 or less or 8 or more
  - Bence Jones proteinuria positive from 24-h urine sample
  - Peripheral blood circulating plasma cells > 5 × 106/L
- **Immunophenotyping Characterization and Immunoparesis**
  - ≥ 95% of aberrant plasma cells by flow within the plasma cell bone marrow compartment plus
  - Immunoparesis (> 25% decrease in one or both uninvolved immunoglobulins relative to the lowest normal value)
- **Cytogenetic Abnormalities**
  - Presence of t(4;14)
  - Presence of del17p
  - Gains of 1q24
  - Hyperdiploidy
  - Gene Expression Profiling risk score > -0.26
- **Pattern of serum M-Component Evolution**
  - Evolving type: if M-protein ≥ 3 g/dL, increase of at least 10% within the first 6 months. If M-protein < 3 g/dL, annual increase of M-protein for 3 years
  - Increase in the M-protein to ≥ 3 g/dL over the three months since the previous determination
- **Imaging Assessments**
  - MRI: Radiologic progressive disease (MRI-PD) was defined as newly detected focal lesions (FLs) or increase in diameter of existing FL and a novel or progressive diffuse infiltration.
  - Positive PET/CT with no underlying osteolytic lesion

Abbreviations: MM, multiple myeloma; SMM, smoldering multiple myeloma; PET-CT, ^{18}F-fluorodeoxyglucose (FDG) PET/CT.

TABLE 2. Risk Models for the Stratification of SMM

Risk Model		Risk of Progression to MM
Mayo Clinic		**Median TTP (years)**
≥ 10% clonal PCBM infiltration	1 risk factor	10
≥ 3 g/dL of serum M-protein	2 risk factors	5
Serum FLC ratio between < 0.125 or > 8	3 risk factors	1.9
Spanish Myeloma		**Median TTP (years)**
≥ 95% of aberrant PCs by MFC	No risk factor	NR
Immunoparesis	1 risk factor	6
	2 risk factors	1.9
Heidelberg		**3-year TTP**
Tumor mass using the Mayo Model	T-mass low + CA low risk	**15%**
t(4;14), del17p, or +1q	T-mass low + CA high risk	**42%**
	T-mass high + CA low risk	**64%**
	T-mass high + CA high risk	**55%**
SWOG		**2-year TTP**
Serum M-protein ≥ 2 g/dL	No risk factor	30%
Involved FLC > 25 mg/dL	1 risk factor	29%
GEP risk score > −0.26	≥ 2 risk factors	71%
Penn		**2-year TTP**
≥ 40% clonal PCBM infiltration	No risk factor	16%
sFLC ratio ≥ 50	1 risk factor	44%
Albumin ≤ 3.5 mg/dL	≥ 2 risk factors	81%
Japanese		**2-year TTP**
Beta 2-microglobulin ≥ 2.5 mg/L	2 risk factors	67.5%
M-protein increment rate > 1 mg/dL/d		
Czech & Heidelberg		**2-year TTP**
Immunoparesis	No risk factor	5.3%
Serum M-protein ≥ 2.3 g/dL	1 risk factor	7.5%
Involved/uninvolved sFLC > 30	2 risk factors	44.8%
	3 risk factors	81.3%
Barcelona		**2-year TTP**
Evolving pattern = 2 points	0 points	2.4%
Serum M-protein ≥ 3 g/dL = 1 point	1 point	31%
Immunoparesis = 1 point	2 points	52%
	3 points	80%

Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM): novel biological insights and development of early treatment strategies

Neha Korde,[1,2] Sigurdur Y. Kristinsson,[3] and Ola Landgren[1]

[1]Medical Oncology Branch, National Cancer Institute, National Institutes of Health (NIH), Bethesda, MD; [2]Hematology Branch, National Heart, Lung, and Blood Institute, NIH, Bethesda, MD; and [3]Hematology Center, Karolinska University Hospital and Institutet, Stockholm, Sweden

Monoclonal gammopathy of unknown significance (MGUS) and smoldering multiple myeloma (SMM) are asymptomatic plasma cell dyscrasias, with a propensity to progress to symptomatic MM. In recent years there have been improvements in risk stratification models (involving molecular markers) of both disorders, which have led to better understanding of the biology and probability of progression of MGUS and SMM. In the context of numerous molecular events and heterogeneous risk of progression, developing individualized risk profiles for patients with MGUS and SMM represents an ongoing challenge that has to be addressed by prospective clinical monitoring and extensive correlative science. In this review we discuss the current standard of care of patients with MGUS and SMM, the use of risk models, including flow cytometry and free-light chain analyses, for predicting risk of progression. Emerging evidence from molecular studies on MGUS and SMM, involving cytogenetics, gene-expression profiling, and microRNA as well as molecular imaging is described. Finally, future directions for improving individualized management of MGUS and SMM patients, as well as the potential for developing early treatment strategies designed to delay and prevent development of MM are discussed. (*Blood*. 2011; 117(21):5573-5581)

Table 2. Risk stratification schemes for MGUS and SMM

Risk stratification scheme	No. of risk factors	No. of patients (%)	20-year progression, %	RR
Mayo Clinic for MGUS patients[55]	0	449 (38)	5	1
Risk factors: M-protein > 1.5 g/dL, non-IgG MGUS, FLC ratio < 0.26 or > 1.65	1	420 (37)	21	5.4
	2	226 (20)	37	10.1
	3	53 (5)	58	20.8
	Total	1148 (100)	20	N/A
			5-year progression, %	
Spanish study group for MGUS patients[21]	0	127 (46)	2	1
Risk factors: ≥ 95% aPC, DNA aneuploidy	1	133 (48)	10	5
	2	16 (6)	46	23
	Total	276* (100)	8.5	N/A
Mayo Clinic for SMM patients[20]	1	76 (28)	25	1
Risk factors†: marrow plasma cells ≥ 10%, M-protein ≥ 3 g/dL, FLC ratio < 0.125 or > 8	2	115 (42)	51	2.0
	3	82 (30)	76	3.0
	Total	273 (100)	51	N/A
Spanish study group for SMM patients[21]	0	28 (31)	4	1
Risk factors: ≥ 95% aPC, immunoparesis	1	22 (25)	46	11.5
	2	39 (44)	72	18
	Total	89‡ (100)	46	N/A

MGUS indicates monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; RR, relative risk; FLC, free light chain; N/A, not applicable; and aPC, aberrant plasma cell.

*A total of 407 patients with MGUS were studied; 276 patients had available aneuploidy data.

†Patients must have at least one of the first 2 risk factors to meet criteria for SMM.

‡A total of 93 patients with SMM were initially studied; 89 had available immunoparesis data.

- M protein miktarı
- Kemik iliği plazma hücre oranı
- Anormal serbest hafif zincir oranı

Mayo Klinik

- Anormal plazma hücre yüzdesi
- İmmunoparazi

PETHEMA

A. Risk Factors[a]: Marrow Plasma Cells ≥ 10%, M-protein ≥ 3 g/dL, FLC Ratio < 0.125 or > 8

Number of Risk Factors	Number of Patients (%)	5-Year Progression	Relative Risk
1	76 (28)	25%	1
2	115 (42)	51%	2.0
3	82 (30)	76%	3.0
Total	273 (100)	51%	NA

B. Risk Factors: ≥ 95% aPC, Immunoparesis

Number of Risk Factors	Number of Patients (%)	5-Year Progression	Relative Risk
0	28 (31)	4%	1
1	22 (25)	46%	11.5
2	39 (44)	72%	18
Total	89 (100)[b]	46%	NA

RİSKİ BELİRLE
-3 GRUP-

* 1) DÜŞÜK RİSK: Mayo ve ispanyol risk modellerine göre hiçbir risk faktörü taşımayanlar. Beklenen 5 yıllık progresyon %8. MGUS a benzer. Yıllık izlem yeterlidir.
* 2) İNTERMEDİATE RİSK: Bazı risk faktörleri içeren grup. Beklenen 5 yıllık progresyon %42 . 6 ayda bir izlem gereklidir.
* 3) YÜKSEK RİSK: Risk modellerinden en az bir risk faktörüne sahip hastalar . %50 si 2 yıl içinde progrese olur. Bu yüzden 2-3 ay aralıklarla takip edilmelidir.

Clinical Course and Prognosis of Smoldering (Asymptomatic) Multiple Myeloma

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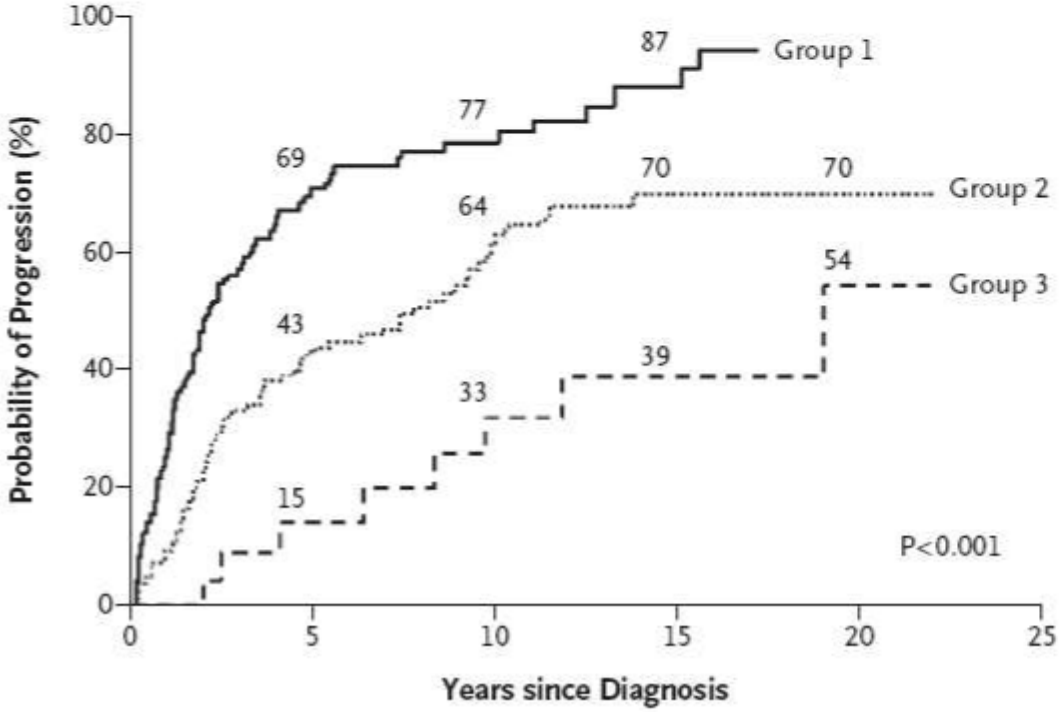

Grup 1 **Kİ plazma hücresi ≥ %10**
MP≥ 3 gr/dl

Grup 2 **Kİ plazma hücresi ≥ %10**
MP< 3 gr/dl

Grup 3 **Kİ plazma hücresi < %10**
MP≥ 3 gr/dl

n=2131
163 olguda ilerleyici hastalık (%59)

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Serum free light chain ratio as a biomarker for high-risk smoldering multiple myeloma

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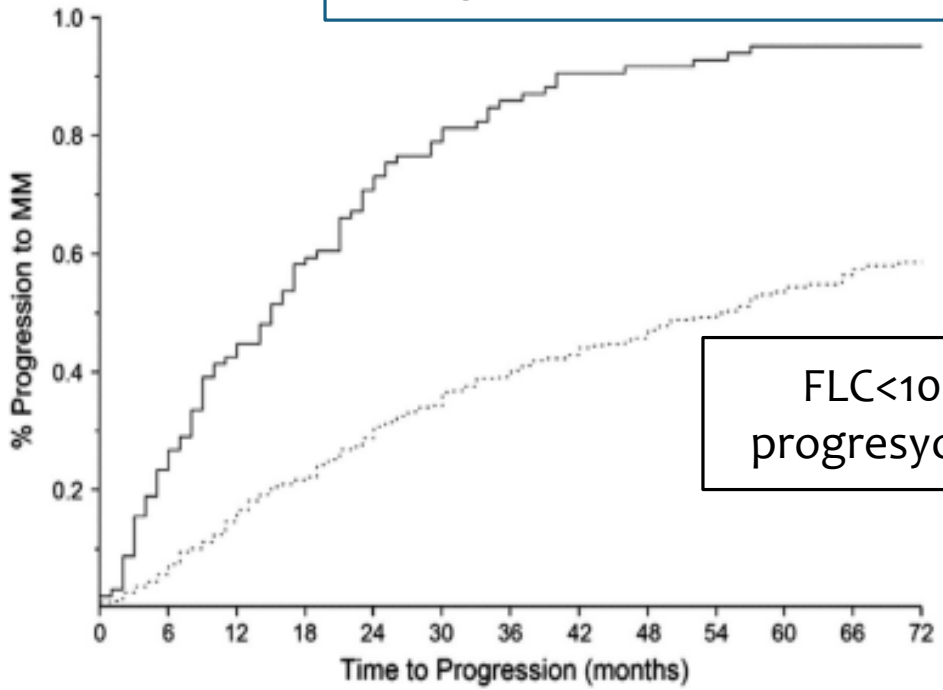
[3]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Abstract

A markedly elevated serum free light chain (FLC) ratio may serve as a biomarker for malignant transformation in high-risk smoldering multiple myeloma (SMM) and identify patients who are at imminent risk of progression. We retrospectively studied the predictive value of the serum (FLC) assay in 586 patients with SMM diagnosed between 1970 to 2010. A serum involved/uninvolved FLC ratio ≥100 was used to define high-risk SMM, which included 15% ($n = 90$) of the total cohort. Receiver operating characteristics analysis determined the optimal FLC ratio cut-point to predict progression to symptomatic multiple myeloma (MM) within 2 years of diagnosis, which resulted in a specificity of 97% and sensitivity of 16%. Fifty-six percent of patients developed progressive disease during median follow-up of 52 months, but this increased to 98% in the subgroup of patients with FLC ratio ≥100. The median time to progression in the FLC ratio ≥100 group was 15 months versus 55 months in the FLC <100 group ($P<0.0001$). The risk of progression to MM within the first 2 years in patients with an FLC ratio ≥100 was 72%; the risk of progression to MM or light chain amyloidosis in 2 years was 79%. We conclude that a high FLC ratio ≥100 is a predictor of imminent progression in SMM, and such patients may be considered candidates for early treatment intervention.

FLC> 100 ‘ de myeloma progresyon ortalama 15 ay



FLC<100 ‘de myeloma progresyon ortalama 55 ay

Figure 2.

TTP to symptomatic multiple myeloma from initial involved/uninvolved FLC ratio of ≥100 versus a ratio of <100. Median TTP was 15 months in the FLC ratio ≥100 group compared with 55 months in the FLC ratio <100 group (P<0.0001). At 24 months, 72% of patients with FLC ratio ≥100 had progressed to MM versus 28% of patients with FLC ratio <100.

2.Yılda FLC>100 = %72
FLC<100=%28 ‘i myelom…

Diğer risk faktörleri?

* M protein miktarı yüksekliği
* kemik iliği plazma hücre oranı yüksekliği
* serbest hafif zincir yüksekliği
* BAŞKA?

Genetik profili

Published in final edited form as:
Leukemia. 2013 August ; 27(8): 1738–1744. doi:10.1038/leu.2013.86.

Impact of primary molecular cytogenetic abnormalities and risk of progression in smoldering multiple myeloma

SV Rajkumar[1], **V Gupta**[1], **R Fonseca**[2], **A Dispenzieri**[1], **WI Gonsalves**[1], **D Larson**[3], **RP Ketterling**[4], **JA Lust**[1], **RA Kyle**[1], and **SK Kumar**[1]

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Abstract

We studied 351 patients with smoldering multiple myeloma (SMM) in whom the underlying primary molecular cytogenetic subtype could be determined based on cytoplasmic immunoglobulin fluorescent in situ hybridization studies. Hundred and fifty-four patients (43.9%) had trisomies, 127 (36.2%) had immunoglobulin heavy chain (IgH) translocations, 14 (4%) both

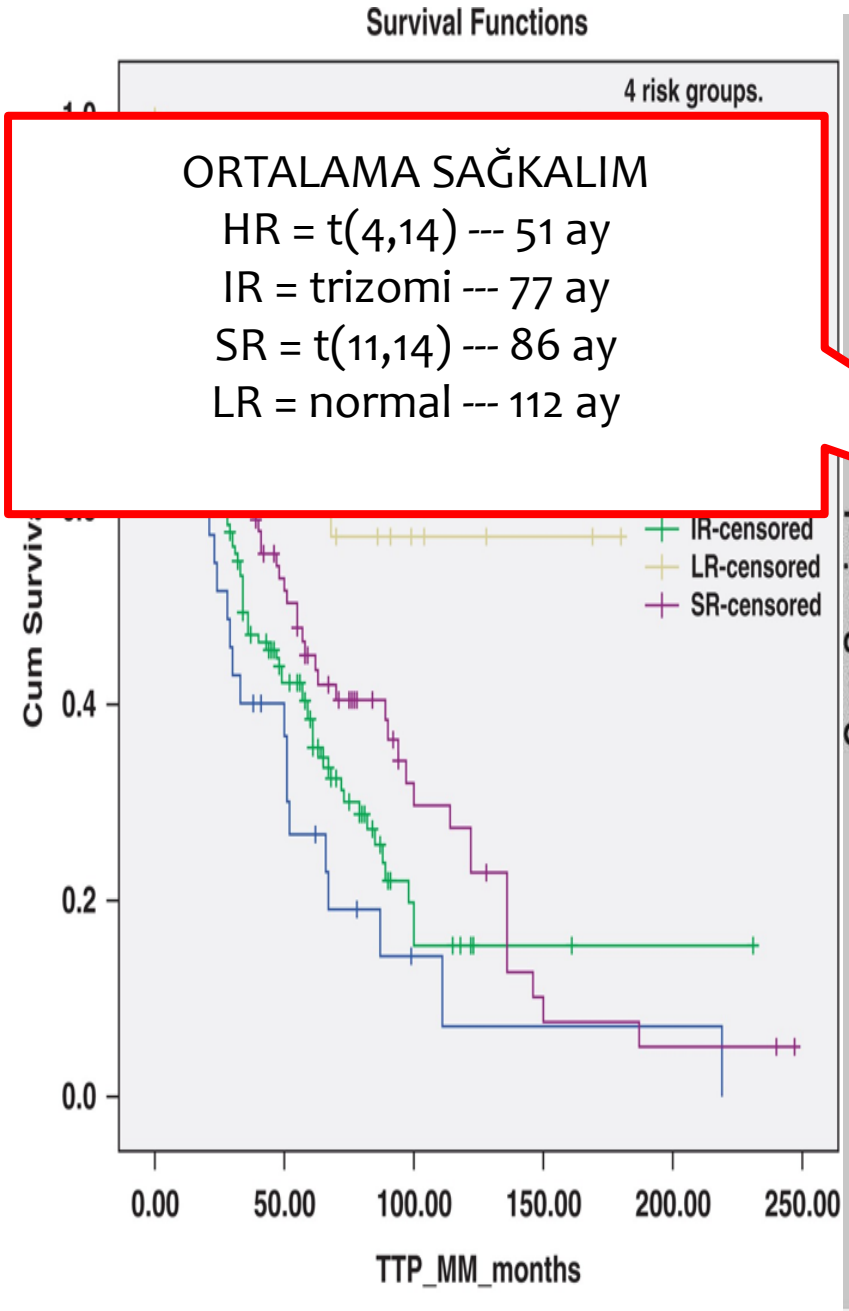
ORTALAMA SAĞKALIM

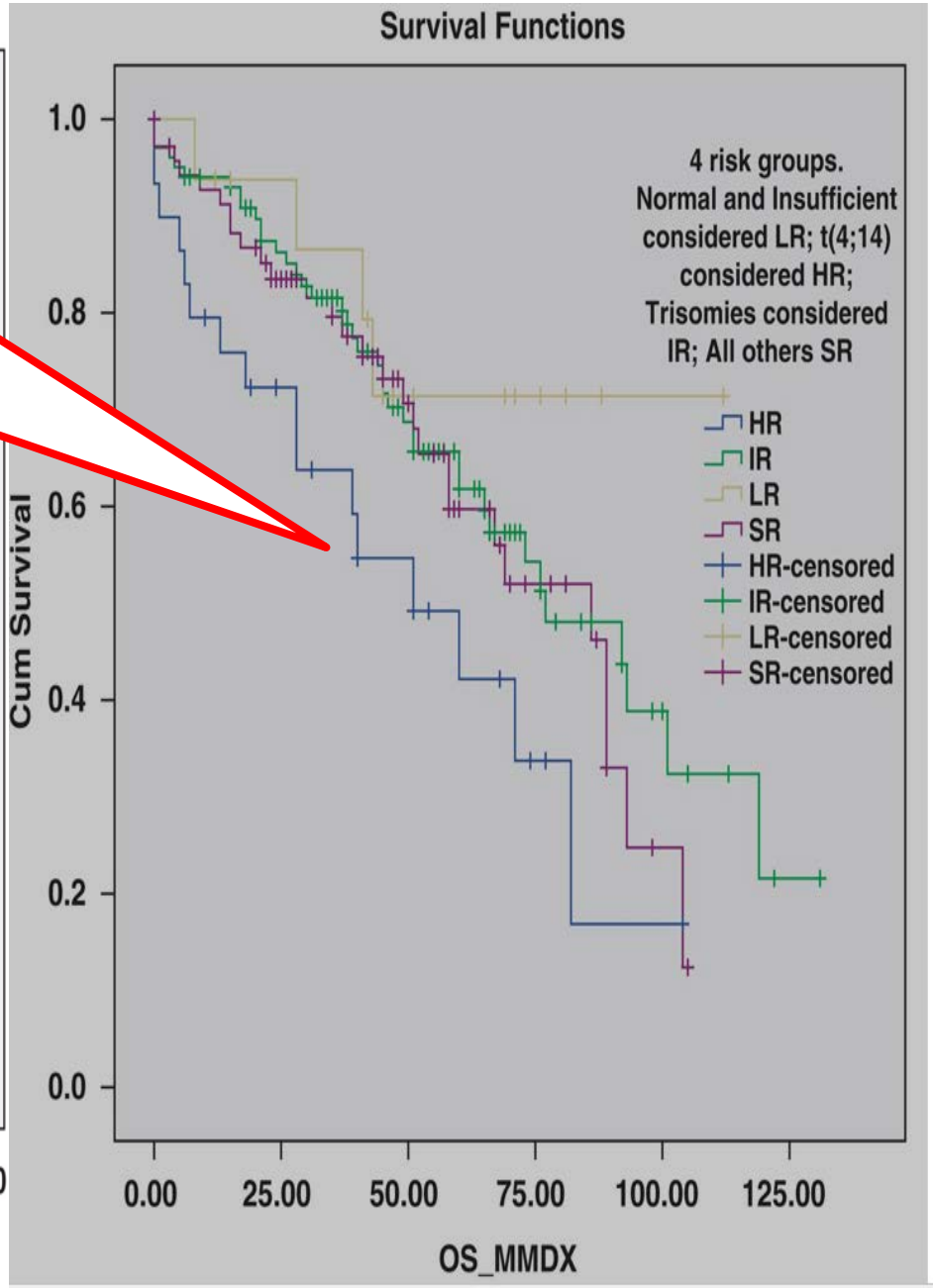
HR = t(4,14) --- 51 ay

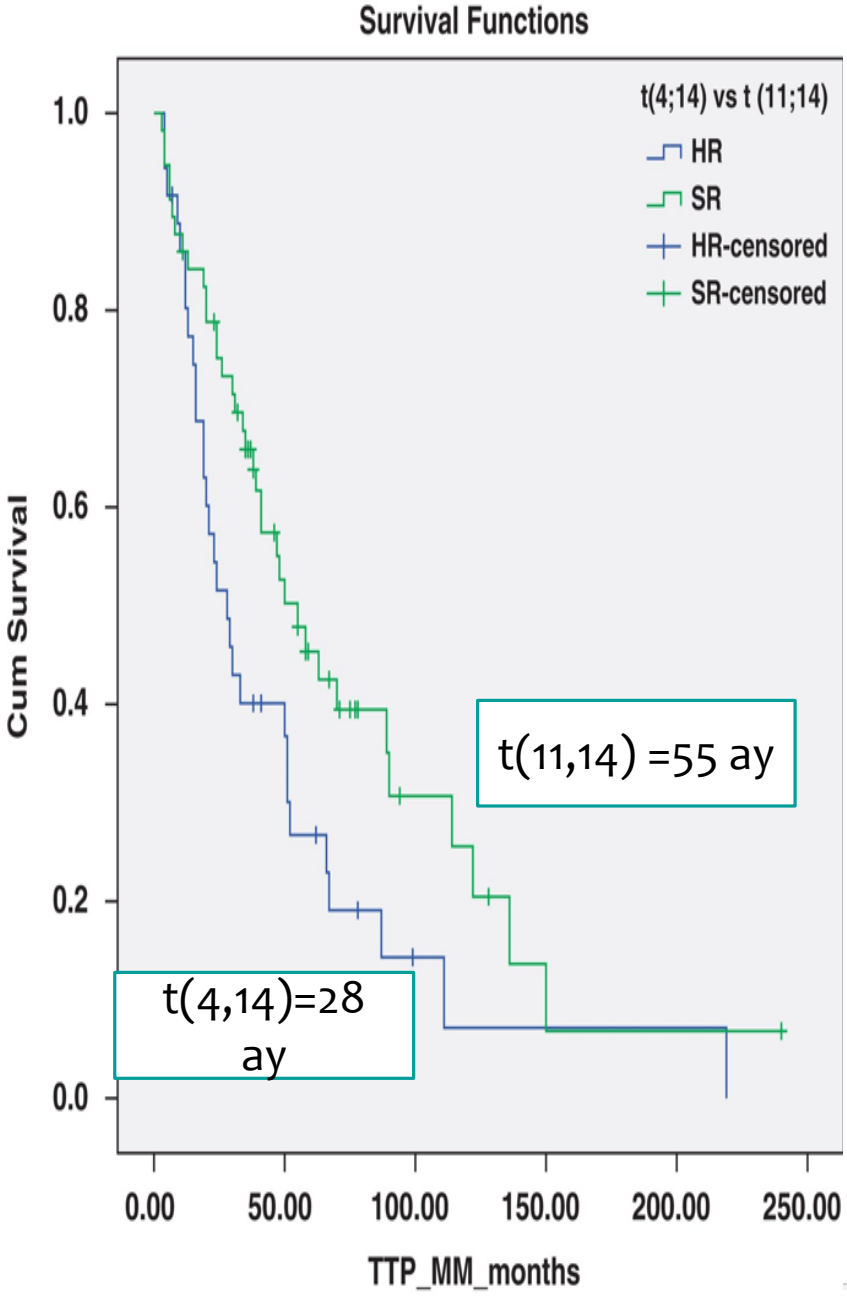
IR = trizomi --- 77 ay

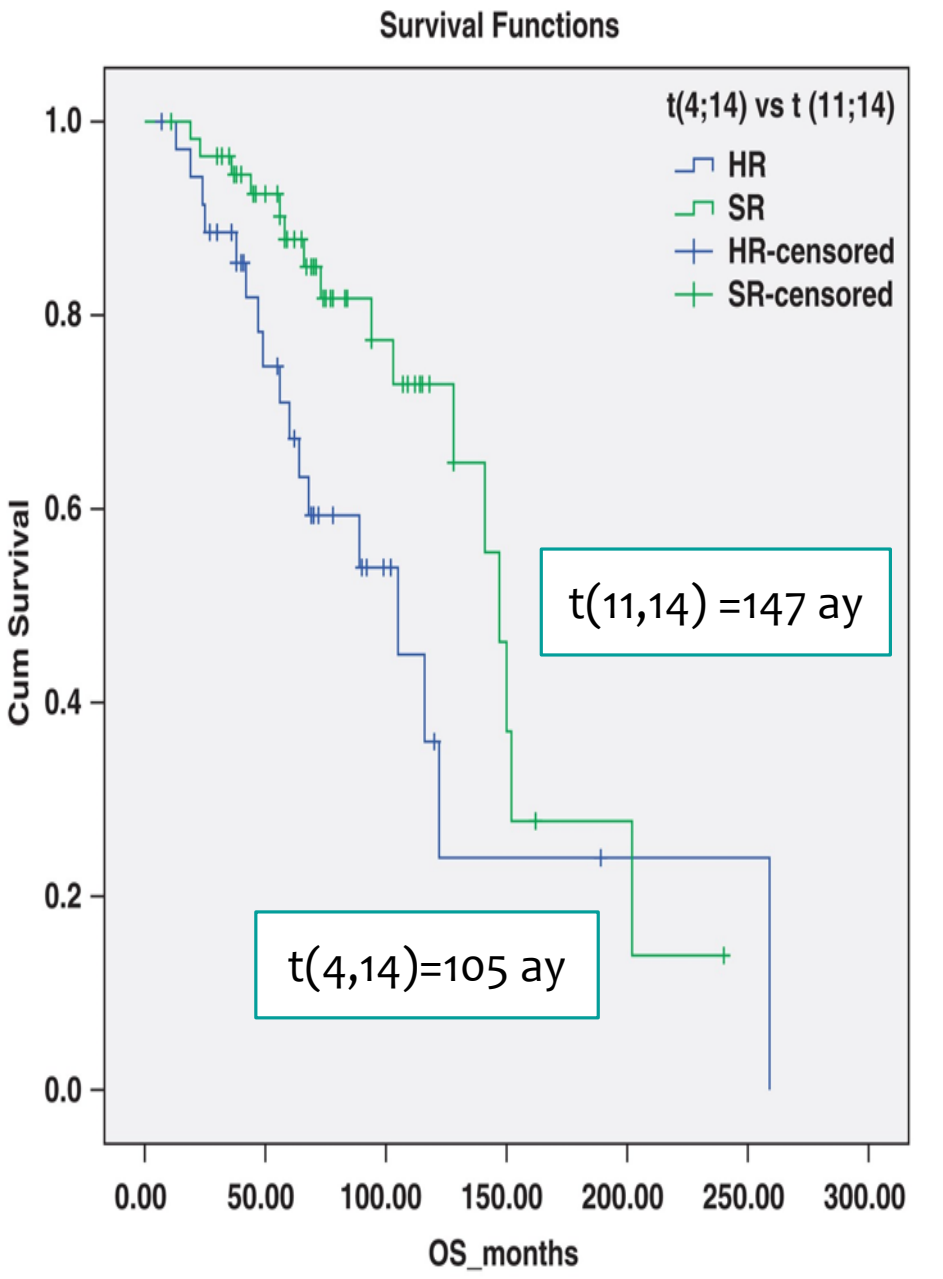
SR = t(11,14) --- 86 ay

LR = normal --- 112 ay






Survival Functions
t(4;14) vs t (11;14)
HR
SR
HR-censored
SR-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0.00
50.00
100.00
150.00
200.00
250.00
TTP_MM_months
t(11,14) =55 ay
t(4,14)=28 ay


Survival Functions
t(4;14) vs t (11;14)
HR
SR
HR-censored
SR-censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0.00
50.00
100.00
150.00
200.00
250.00
300.00
OS_months
t(11,14) =147 ay
t(4,14)=105 ay

Anormal plazma hücre oranı

Report of the European Myeloma Network on multiparametric flow cytometry in multiple myeloma and related disorders A.C. Rawstron et al.

NORMALİ

ANORMAL PLAZMALAR

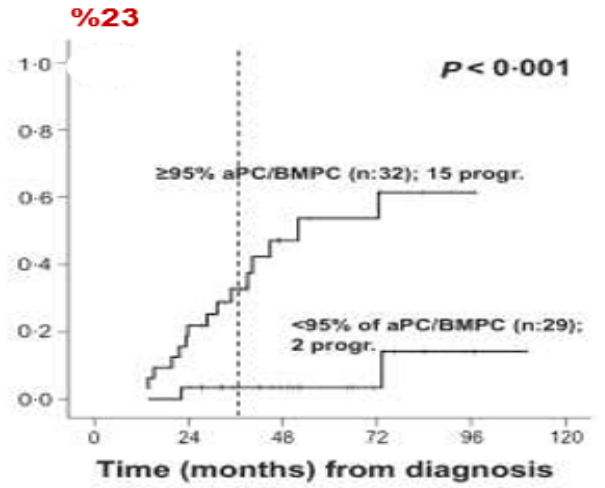
Antigen	*Normal expression profile (percentage expression on normal plasma cells)*	*Abnormal expression profile*	*Percentage of myeloma cases with abnormal expression*	*Require for diag and moni*
CD19	Positive (>70%)	Negative	95%	Essential
CD56	Negative (<15%)	Strongly positive	75%	Essential
CD117	Negative (0%)	Positive	30%	Recommended
CD20	Negative (0%)	Positive	30%	Recommended
CD28	Negative/weak (<15%	Strongly positive	15-45%	Recommended
CD27	Strongly positive (100%)	Weak or negative	40-50%	Recommended
CD81	Positive (100%)	Weak or negative	Not publishe	Suggested
CD200	Weakly positive	Strongly positive	Not publishe	Suggested

haematologica | 2008; 93(3)

Anormal plazma hücre oranı

bjh short report

Risk of progression in smouldering myeloma and monoclonal gammopathies of unknown significance: comparative analysis of the evolution of monoclonal component and multiparameter flow cytometry of bone marrow plasma cells



SMM li 61 hasta aPC>%95 olan 32 hastanın 15 i MM a, aPC<%95 olan 29 hastanın ise sadece 2 si MM a progrese olmuş

Anormal plazma hücreleri : CD19/CD45 (-) ; CD56 (+) ; CD38 zayıf

 British Journal of Haematology, 148, 110–114

Anormal plazma hücre oranı

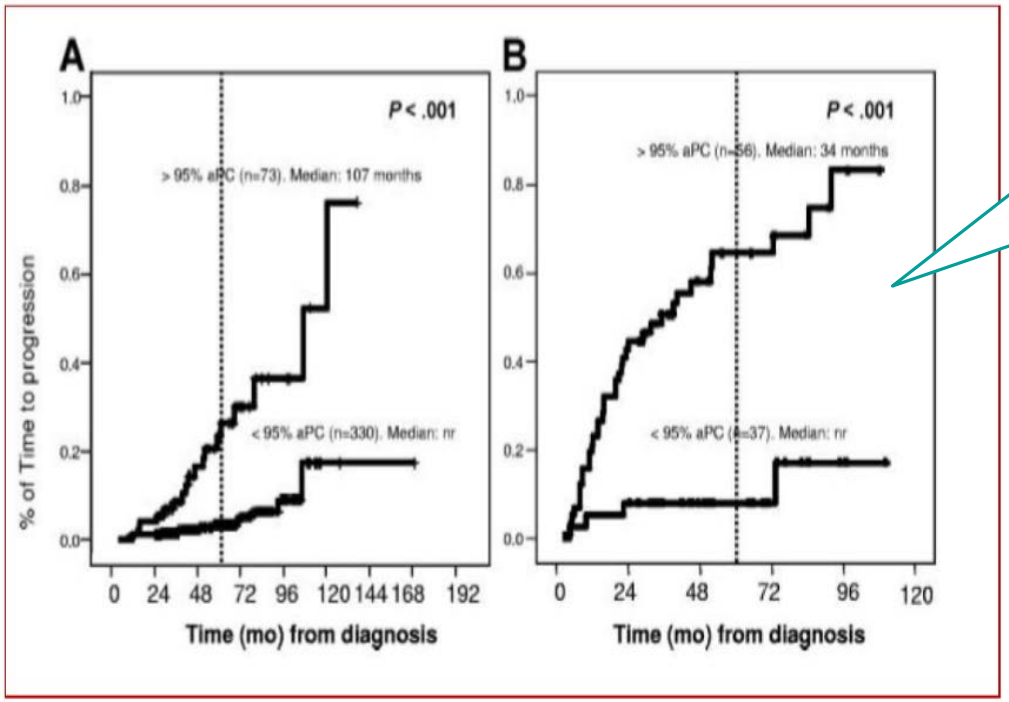
blood

New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells

Ernesto Pérez-Persona,[1] María-Belén Vidriales,[1,2] Gema Mateo,[1] Ramón García-Sanz,[1,2] María-Victoria Mateos,[1] Alfonso García de Coca,[3] Josefina Galende,[4] Guillermo Martín-Nuñez,[5] José M. Alonso,[6] Natalia de las Heras,[7] José M. Hernández,[8] Alejandro Martín,[9] Consuelo López-Berges,[1] Alberto Orfao,[2,10] and Jesús F. San Miguel[1,2]

BLOOD, 1 OCTOBER 2007 • VOLUME 110, NUMBER 7

MGUS=407
SM=93



SMM 93 hasta, aPC>%95 olan 56 hastanın TTP : 34 ay, aPC<%95 37 hastada TTP henüz ulaşılamamış

OPEN

Citation: Blood Cancer Journal (2016) **6**, e454; doi:10.1038/bcj.2016.65

www.nature.com/bcj

ORIGINAL ARTICLE

Evolving changes in disease biomarkers and risk of early progression in smoldering multiple myeloma

P Ravi[1], S Kumar[2], JT Larsen[2], W Gonsalves[2], F Buadi[2], MQ Lacy[2], R Go[2], A Dispenzieri[2], P Kapoor[2], JA Lust[2], D Dingli[2], Y Lin[2], SJ Russell[2], N Leung[2], MA Gertz[2], RA Kyle[2], PL Bergsagel[3] and SV Rajkumar[2]

We studied 190 patients with smoldering multiple myeloma (SMM) at our institution between 1973 and 2014. Evolving change in monoclonal protein level (eMP) was defined as ⩾10% increase in serum monoclonal protein (M) and/or immunoglobulin (Ig) (M/Ig) within the first 6 months of diagnosis (only if M-protein ⩾3 g/dl) and/or ⩾25% increase in M/Ig within the first 12 months, with a minimum required increase of 0.5 g/dl in M-protein and/or 500 mg/dl in Ig. Evolving change in hemoglobin (eHb) was defined as ⩾0.5 g/dl decrease within 12 months of diagnosis. A total of 134 patients (70.5%) progressed to MM over a median follow-up of 10.4 years. On multivariable analysis adjusting for factors known to predict for progression to MM, bone marrow plasma cells ⩾20% (odds ratio (OR) = 3.37 (1.30–8.77), $P = 0.013$), eMP (OR = 8.20 (3.19–21.05), $P < 0.001$) and eHb (OR = 5.86 (2.12–16.21), $P = 0.001$) were independent predictors of progression within 2 years of SMM diagnosis. A risk model comprising these variables was constructed, with median time to progression of 12.3, 5.1, 2.0 and 1.0 years among patients with 0–3 risk factors respectively. The 2-year progression risk was 81.5% in individuals who demonstrated both eMP and eHb, and 90.5% in those with all three risk factors.

Blood Cancer Journal (2016) **6,** e454; doi:10.1038/bcj.2016.65; published online 29 July 2016

* 1973- 2014 arası 190 SMM hastası
* Ortalama 10.4 yıllık izlemde 134 ‘ü (%70,5) MM a progrese olmuş
* Bağımsız prediktif risk faktörleri: Mproteininde , Hb de gelişen değişiklikler , kemik iliği plz hücresi≥ %20

* M protein değişikliği:
  ilk 6 ayda ≥ %10
  (m proteini≥ 3 g/dl olmalı)
  ilk 12 ayda ≥%25 artış
  (herhangi seviye m proteini ,min 0,5 gr artış olmalı)
* Hb değişikliği:
  12 ayda ≥ 0,5 g/dl düşme

* Median TTP:
* 0 risk : 12.3 yıl
* 1 risk: 5.1 yıl
* 2 risk: 2.0 yıl
* 3 risk: 1.0 yıl

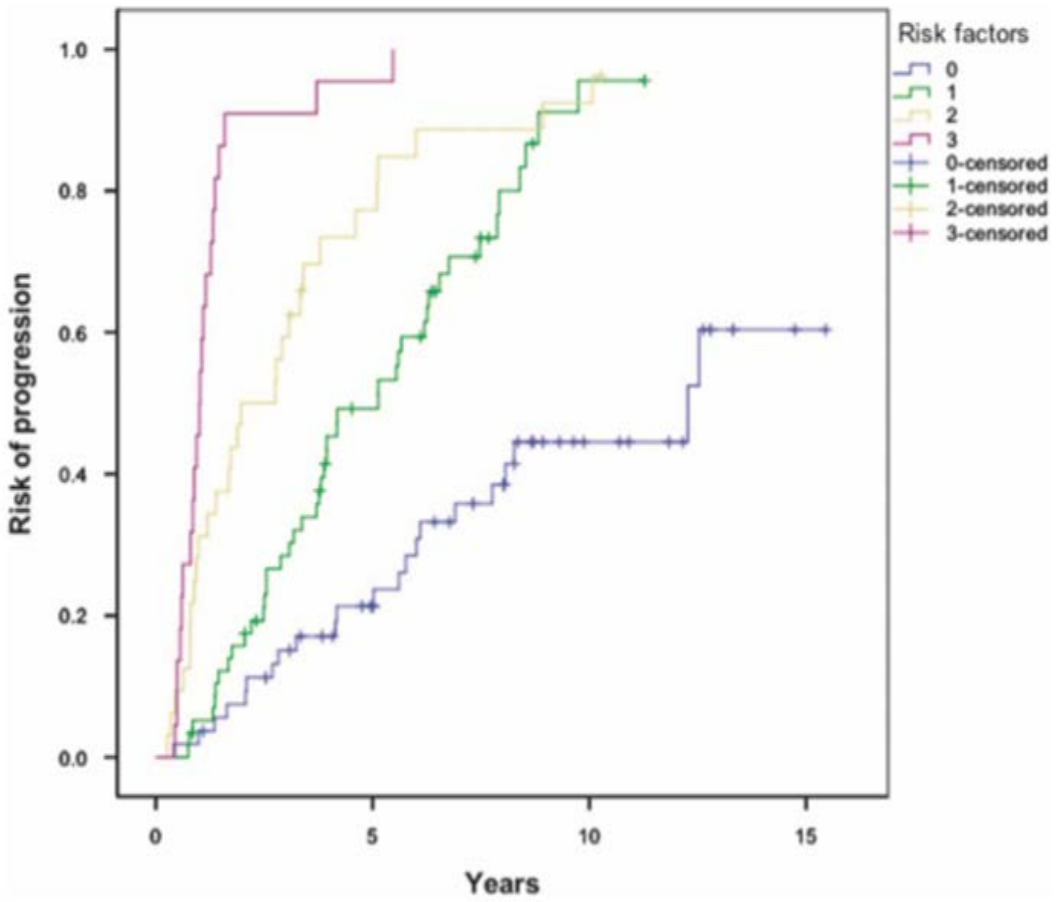
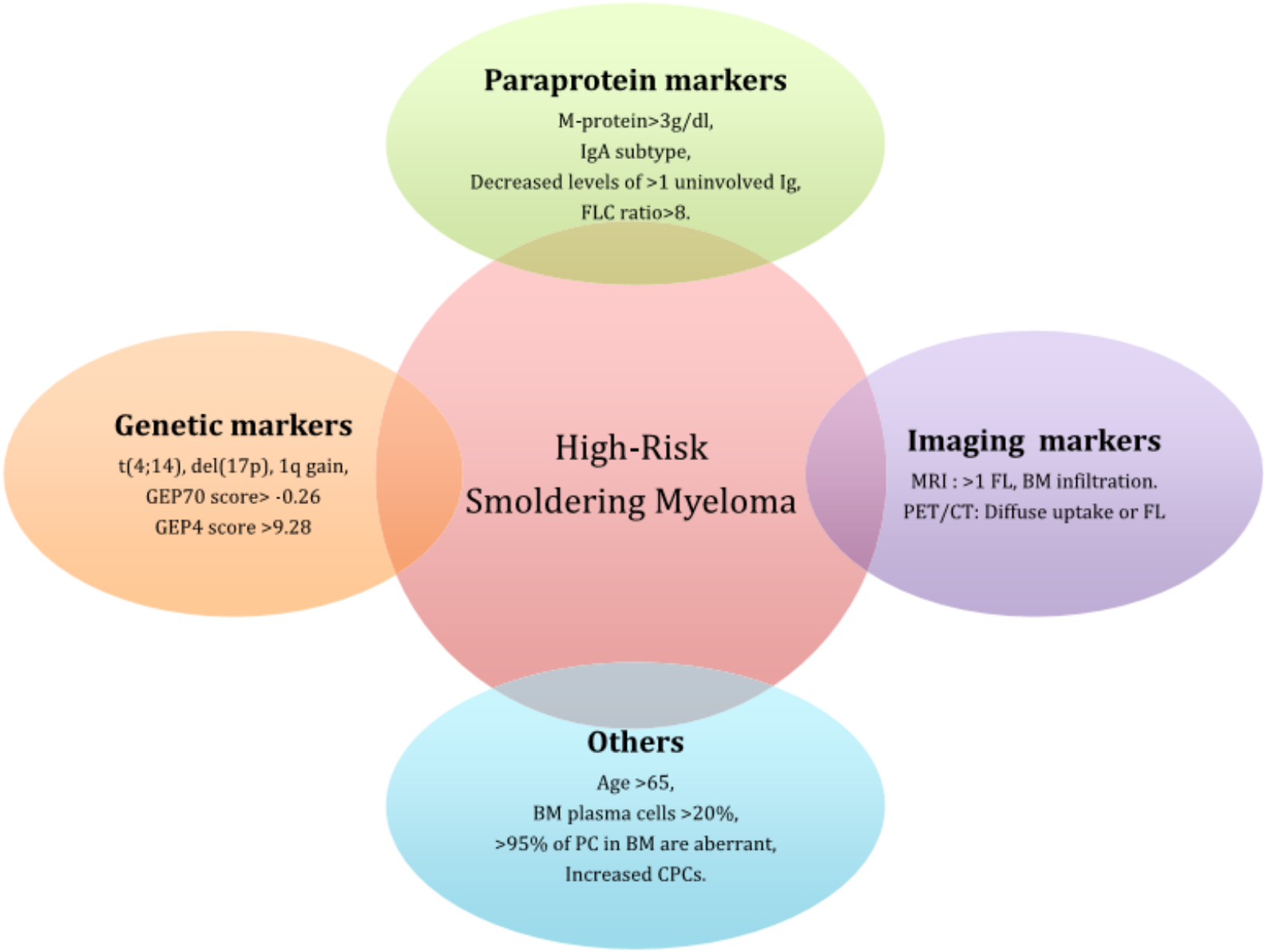


Figure 1. Risk of progression in SMM patients, stratified by the number of risk factors (eMP, eHb and BMPC $\geqslant 20\%$) at diagnosis. $P < 0.001$.

* Mproteini ve Hb değişikliğini birlikte gösterenlerin 2 yıllık progresyon riski %81.5

* Her üç riski içeren hastalarda 2 yıllık progresyon riski % 90.5


Paraprotein markers
M-protein>3g/dl,
IgA subtype,
Decreased levels of >1 uninvolved Ig,
FLC ratio>8.
Genetic markers
t(4;14), del(17p), 1q gain,
GEP70 score> -0.26
GEP4 score >9.28
High-Risk
Smoldering Myeloma
Imaging markers
MRI : >1 FL, BM infiltration.
PET/CT: Diffuse uptake or FL
Others
Age >65,
BM plasma cells >20%,
>95% of PC in BM are aberrant,
Increased CPCs.

TEDAVİ EDELİM Mİ?

Table 3. Selected clinical studies of strategies to prevent progression of SMM, MGUS, and early-stage multiple myeloma

Reference	Study design	Intervention	No. of patients	Outcome/comment
Hjorth 1993[48]	Randomized controlled trial	Initial vs deferred MP therapy	50 SMM and IMM (25/25)	Similar response rate, response duration, and survival
Rajkumar 2001[56]	Single-arm pilot study	Thalidomide	16 SMM and IMM	MR or better in 11/16; microvessel density did not predict response
Musto 2008[50]	Open-label, randomized controlled trial	Zoledronate	163 SMM (81/82)	Zoledronate for 1 y decreased risk of skeletal-related disease, but TTP was similar ($P = .83$)
Barlogie 2008[49]	Single-arm phase 2 trial	Thalidomide/pamidronate	76 SMM	Median TTP 7 y; PR identifies subset requiring earlier salvage therapy for symptomatic disease
Lust 2009[57]	Single-arm phase 2 trial	Anakinra (IL-1 receptor antagonist)	47 SMM and IMM (25 received anakinra and DEX)	Median PFS was 37.5 mo MR (n = 3), PR (n = 5); 8 patients stable on drug for 4 y
Golombick 2009[58]	Single-blind, randomized, crossover pilot study	Curcumin vs placebo	26 MGUS	5 of 10 patients with M-protein > 2 g/dL had decreased M-protein (12%-30% reduction)
Kalaycio 2004-ongoing[59]	Double-blind, randomized controlled trial	Celoxicib vs placebo	36 MGUS and SMM	Aim: to test whether celoxicib reduces the M-protein concentration
Mateos 2007-ongoing[60]	Open-label randomized controlled trial	Lenalidomide + DEX vs observation	120 "high-risk" SMM	Aim: to evaluate whether lenalidomide + DEX extends TTP
Ballester 2009-ongoing[61]	Unblinded, nonrandomized trial	Omega-3 fatty acids	48 MGUS, SMM, or CLL*	Aim: to assess whether omega-3 fatty acids reduce activated NF-κB levels in peripheral blood lymphocytes
Zonder 2009-ongoing[62]	Single-arm pilot study	Green tea extract	17 MGUS or SMM*	Aim: to test whether green tea extract reduces the M-protein concentration
Lonial 2010-ongoing[63]	Open-label randomized controlled trial	Lenalidomide vs observation	370 "high-risk" SMM*	Aim: to evaluate whether lenalidomide extends TTP
Landgren 2010-ongoing[64]	Single-arm phase 2 trial	Anti-KIR monoclonal antibody	21 SMM	Aim: to evaluate whether anti-KIR reduces the M-protein concentration > 50% from baseline

Adapted from Waxman et al.[54]

SMM indicates smoldering multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; MP, melphalan/prednisone; IMM indolent multiple myeloma (asymptomatic but with evidence of end-organ damage); MR, minor response (25%-50% decrease in M-protein); TTP, time to progression; DEX, dexamethasone; PFS, progression-free survival; and PR, partial response (≥ 50% decrease in M-protein).

*Estimated enrollment

50 hasta
asemptomatik myelom
ileriye dönük & rastgellenmiş bir çalışma

Birinci kol tanı anında MP
İkinci kol progresyon durumunda MP

Yanıt oranı
Yanıt süresi
Sağkalım

FARKSIZ

Eur J Haematol 1993;50(2):95-102

Table 3. Selected clinical studies of strategies

Reference		
Hjorth 1993[48]	Randomized controlled trial	therapy
Rajkumar 2001[56]	Single-arm pilot study	Thalidomide
Musto 2008[50]	Open-label, randomized controlled trial	Zoledronate
Barlogie 20	Single-arm trial	Thalidomide/par

5 of 10 patients with M-protein > 2 g/dL had decreased M-protein (12%-30% reduction)

MM — Aim: to test whether celoxicib reduces the M-

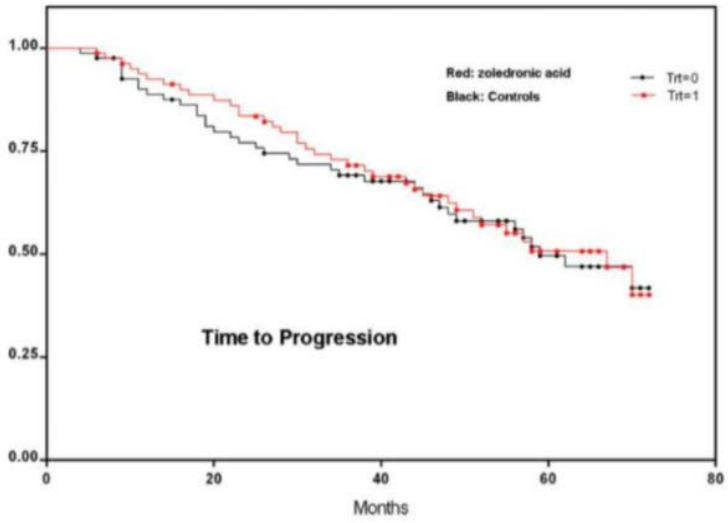
matik myelom
gün, maksimum doz 800 mg/gün
%69

sk" SMM* — Aim: to evaluate whether lenalidomide extends TTP

Aim: to evaluate whether anti-KIR reduces the M-protein concentration > 50% from baseline

ificance; MP, melphalan/prednisone; IMM indolent multiple myeloma
M-protein); TTP, time to progression; DEX, dexamethasone; PFS,

A Multicenter, Randomized Clinical Trial Comparing Zoledronic Acid Versus Observation in Patients With Asymptomatic Myeloma



CANCER October 1, 2008 / Volume 113 / Number 7

Early versus deferred treatment for early stage multiple myeloma (Review)

He Y, Wheatley K, Glasmacher A, Ross H, Djulbegovic B

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2003, Issue 1

http://www.thecochranelibrary.com

WILEY

Main results

Three trials were included with a total of 131 patients in each of the early treatment and deferred treatment groups. Early MM is asymptomatic stage I in these trials. All trials used standard Melphalan treatment but not stem cell transplantation. No statistically significant heterogeneity among the studies was detected. Beneficial effects of early treatment were seen in delay of myeloma progression (Peto's OR = 0.16, 95% CI: 0.09 to 0.29), and reduced vertebral compression (OR = 0.18, 95%CI: 0.02 to 1.59, NNT = 23, 95% CI: an NNT of 11, via infinity, to an NNH of 50). No significant effects on mortality and response rate were seen (Peto's OR = 1.11, 95% CI: 0.67 to 1.84, and OR = 0.63, 95% CI: 0.33 to 1.23, respectively). Early treatment may increase the risk of acute leukemia (Peto's OR = 3.20, 95% CI: 0.55 to 18.73, NNH = 44, 95% CI: an NNT of 63, via infinity, to an NNH of 15).

* 3 çalışma, toplam 131 hasta,Melfalan tedavisi
* Erken tedavi myeloma progresyonda ve vertebral bası azaltılmasında faydalı bulunmuş
* Mortalite ve tedaviye cevap oranları aynı
* Erken tedavinin akut lösemi gelişim riskini artırdıgı görülmüş.

Early versus Deferred Treatment for Smoldering Multiple Myeloma: A Meta-Analysis of Randomized, Controlled Trials

Minjie Gao[1☯], Guang Yang[1☯], Van S. Tompkins[2], Lu Gao[1], Xiaosong Wu[1], Yi Tao[1], Xiaojing Hu[1], Jun Hou[1], Ying Han[1], Hongwei Xu[3], Fenghuang Zhan[3*], Jumei Shi[1*]

1 Department of Hematology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China, 2 Department of Pathology, University of Iowa Carver College of Medicine, Iowa City, Iowa, United States of America, 3 Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, Iowa, United States of America

Abstract

Purpose: Whether patients with smoldering
remains controversial. Herein, we conducted
deferred treatment for patients with SMM.

Methods: MEDLINE and Cochrane Library we
the effect of early treatment over deferred t
measures were progression, response rate, and adverse events.

Results: Overall, 5 trials including 449 patients were identified. There was a markedly reduced risk of disease progression with early treatment (Odds Ratio [OR] = 0.13, 95% confidence interval [CI] = 0.07 to 0.24). There were no significant differences in mortality and response rate (OR = 0.85, 95% CI = 0.45 to 1.60, and OR = 0.63, 95% CI = 0.32 to 1.23, respectively). More patients in the early treatment arm experienced gastrointestinal toxicities (OR = 10.02, 95%CI = 4.32 to 23.23), constipation (OR = 8.58, 95%CI = 3.20 to 23.00) and fatigue or asthenia (OR = 2.72, 95%CI = 1.30 to 5.67). No significant differences were seen with the development of acute leukemia (OR = 2.80, 95%CI = 0.42 to 18.81), hematologic cancer (OR = 2.07, 95%CI = 0.43 to 10.01), second primary tumors (OR = 3.45, 95%CI = 0.81 to 14.68), nor vertebral compression (OR = 0.18, 95%CI = 0.02 to 1.59).

Conclusions: Early treatment delayed disease progression but increased the risk of gastrointestinal toxicities, constipation and fatigue or asthenia. The differences on vertebral compression, acute leukemia, hematological cancer and second primary tumors were not statistically significant. Based on the current evidence, early treatment didn't significantly affect mortality and response rate. However, further much larger trials were needed to provide more evidence.

5 çalışma, 449 hastanın metaanalizi
Tedavi kollları alkilleyici ve IMID ler

Citation: Gao M, Yang G, Tompkins VS, Gao L, Wu X, et al. (2014) Early versus Deferred Treatment for Smoldering Multiple Myeloma: A Meta-Analysis of Randomized, Controlled Trials. PLoS ONE 9(10): e109758. doi:10.1371/journal.pone.0109758

Editor: Zhenyu Li, University of Kentucky, United States of America

Received April 11, 2014; **Accepted** September 4, 2014; **Published** October 3, 2014

Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and its Supporting Information files.

Funding: This study was supported by grants from the National Natural Science Foundation of China (No. 81372391, 81071856 to J.S., 81000199 to X.H., 81250110552 to T.V., and 81228016 to F.Z.), Shanghai Science and Technology Program (No. 12410705100 to J.S.), Shanghai Tenth People's Hospital Funds (No. 040113015 to J.S.). The funders conceived and designed the experiments, contributed reagents/materials/analysis tools, drafted the paper, and read and approved the final paper.

Competing Interests: The authors have declared that no competing interests exist.

* Email: shijumei@hotmail.com (JMS); fenghuang-zhan@uiowa.edu (FHZ)

☯ These authors contributed equally to this work.

Table 1. Characteristics of studies fulfilling inclusion criteria in the meta-analysis.

Author [year]	Disease	Early treatment defined as	Deferred treatment defined as	No. of enrolled/ analyzed patients	Intervention
Hjorth [1993]	SMM	Immediate treatment on diagnosis/randomization	Observation until symptomatic disease progression	E: 25/25 D: 25/25	M: 0.25 mg/kg P: 2 mg/kg d1-4 of 6 w intervals
Riccardi [1994]	SMM	I[illegible] c[illegible]	Observation until symptomatic disease progression	E:38	
Riccardi [2000]	SMM	Immediate treatment on diagnosis/randomization	Observation until symptomatic disease progression	E:75	
Witzig [2013]	SMM	Immediate treatment on diagnosis/randomization	Observation until symptomatic disease [illegible]gression	E:35	
Mateos [2013]	High-risk SMM	Imm[illegible] diagnosis/randomization	[illegible]servation until symptomatic disease progression	E:57	Maintenance (L: 10 mg/d d1-21, a 28 d cycle, 2 y)

alkilleyiciler

İMİDs

- Erken tedavi hastalık progresyonunu geciktiriyor
- GİS toksisitesi tedavi kolunda yüksek
- Vertebral kompreyon,, akut lösemi, ikinci primer tm görülmesinde anlamlı farklılık yok
- Erken tedavi mortalite ve tedaviye cevap oranlarını değiştirmiyor

MM: multiple myeloma; SMM: smouldering myeloma; M: melphalan; P: prednisone; ZLD: zoledronic acid; Thal: thalidomide; L: lenalidomide; Dex: dexamethasone; E: early treatment arm; D: deferred treatment arm; d: day; w: week; y: year.

doi:10.1371/journal.pone.0109758.t001

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

María-Victoria Mateos, M.D., Ph.D., Miguel-Teodoro Hernández, M.D., Pilar Giraldo, M.D., Javier de la Rubia, M.D., Felipe de Arriba, M.D., Ph.D., Lucía López Corral, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., Bruno Paiva, Ph.D., Luis Palomera, M.D., Ph.D., Joan Bargay, M.D., Albert Oriol, M.D., Felipe Prosper, M.D., Ph.D., Javier López, M.D., Ph.D., Eduardo Olavarría, M.D., Ph.D., Nuria Quintana, M.D., José-Luis García, M.D., Joan Bladé, M.D., Ph.D., Juan-José Lahuerta, M.D., Ph.D., and Jesús-F. San Miguel, M.D., Ph.D.

ABSTRACT

Lenalidomide plus dexamethasone versus observation in patients with high-risk smouldering multiple myeloma (QuiRedex): long-term follow-up a randomised, controlled, phase 3 trial

María-Victoria Mateos, Miguel-Teodoro Hernández, Pilar Giraldo, Javier de la Rubia, Felipe de Arriba, Lucía López Corral, Laura Rosiñol, Bruno Paiva, Luis Palomera, Joan Bargay, Albert Oriol, Felipe Prosper, Javier López, José-María Arguiñano, Nuria Quintana, José-Luis García, Joan Bladé, Juan-José Lahuerta, Jesús-F San Miguel

Summary

Background The standard of care for smouldering multiple myeloma is observation. We did the QuiRedex study to compare early treatment with lenalidomide plus dexamethasone with observation in patients with high-risk smouldering multiple myeloma. Here we report the long-term follow-up results of the trial.

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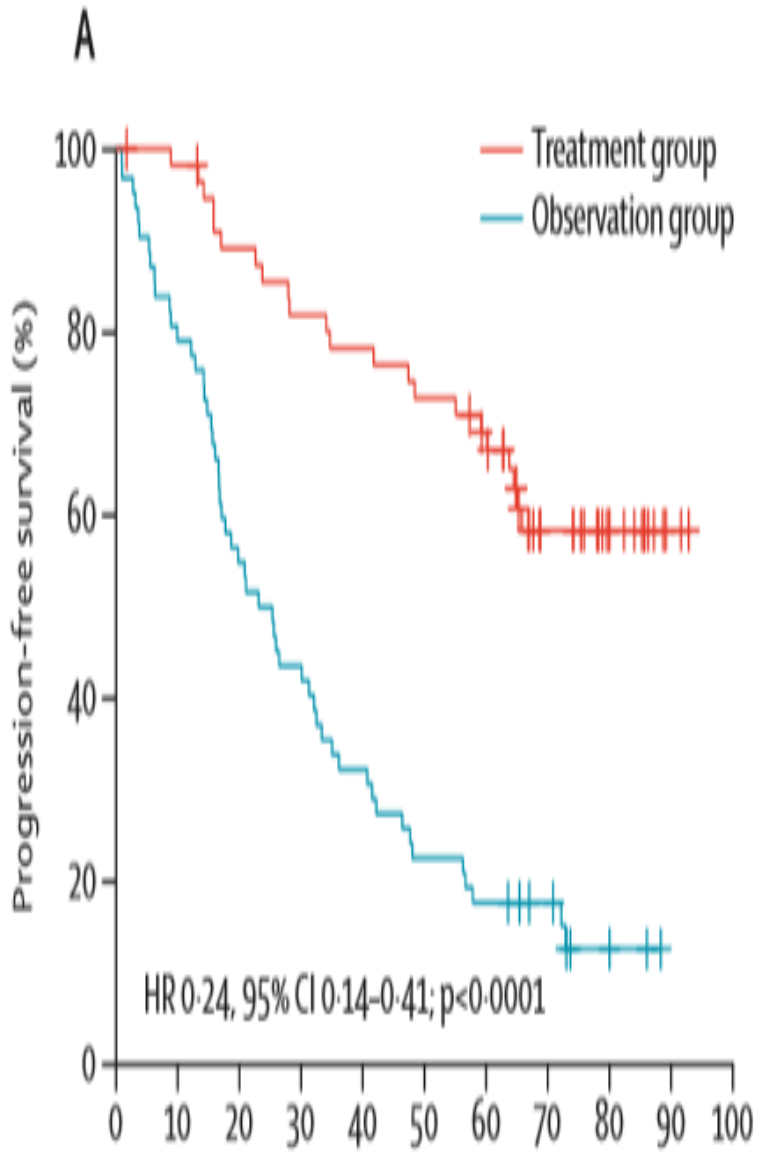
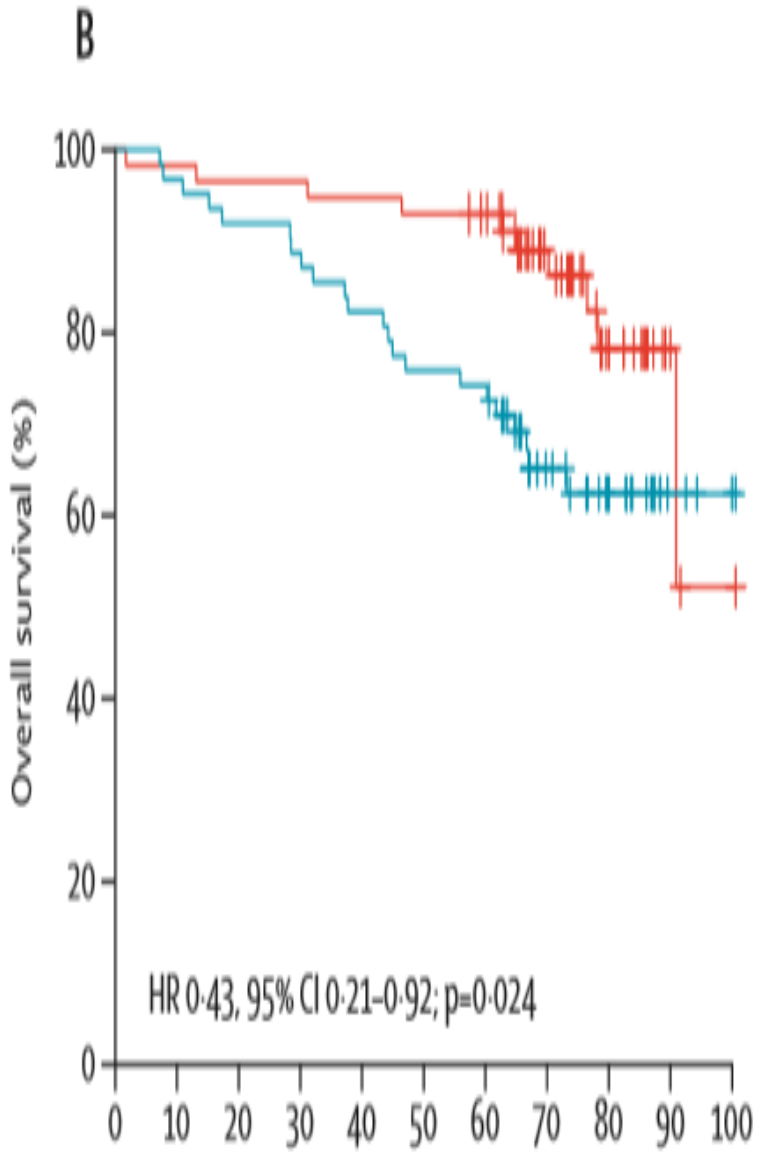
119 hasta	Len+dex (57)	Gözlem (62)	
Median TTP	Not reached	23 ay	
Median OS (çaşılma başlangıcından)	Not reached	Not reached	
Median OS (tanıdan)	117 ay	67 ay	
MM gelişimi	22 hasta(%39)	53 hasta(%86)	
Second primer malıgnıte	6 hasta (%10)	1 hasta (%2)	
ölüm	10 hasta (%18)	22 hasta(%36)	(kümülatif risk aynı)


A
Treatment group
Observation group
Progression-free survival (%)
100
80
60
40
20
0
0 10 20 30 40 50 60 70 80 90 100
HR 0·24, 95% CI 0·14–0·41; p<0·0001


B
Overall survival (%)
100
80
60
40
20
0
0 10 20 30 40 50 60 70 80 90 100
HR 0·43, 95% CI 0·21–0·92; p=0·024

SONUÇ

* Hastalık heterojendir ve risk grubu belirlenmelidir.
* Yüksek risk grubu hastalara konvansiyonel ve yeni ajanlarla erken tedavi çalışmaları yapılmıştır.
* Yeni sonuçlanan çalışmalarda PFS ve OS ajantajları gösterilse de mevcut yaklaşımı değiştirecek güçte ve yeterlilikte şimdilik değildir.
* Şu an için standart yaklaşım GÖZLEM dir.
* Gözlemde takip aralığı hastanın risk grubuna göre yapılmalıdır.(yüksek riskde 2-3 aylık aralarla)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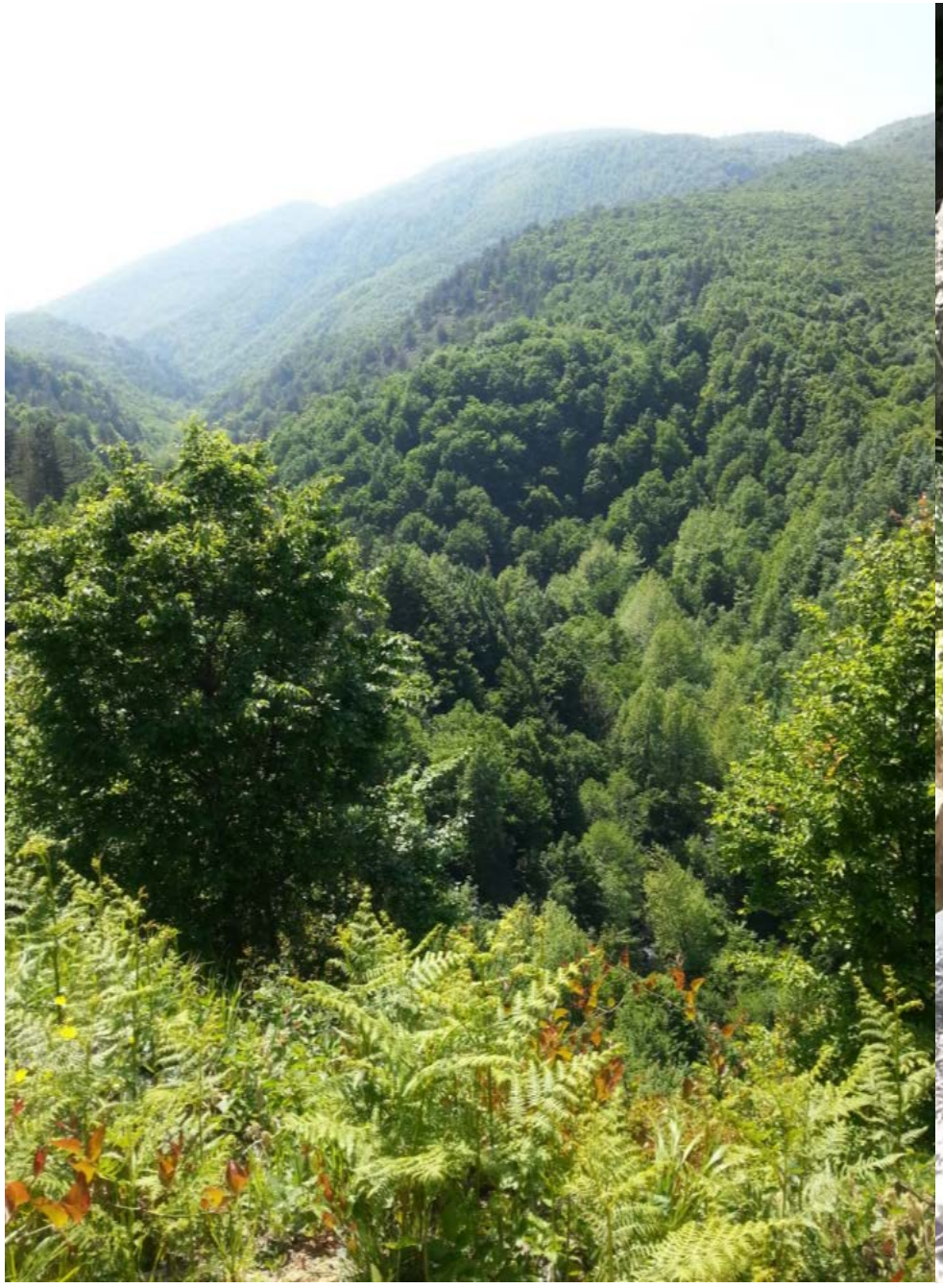

TEŞEKKÜRLER