Early Intervention in Patients with Clonal Hematopoiesis and Increased Risk for Myeloid Malignancies-Are we there yet?

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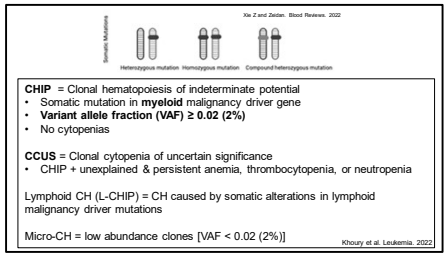
Disclosures

- Consultant for Abbvie, Novartis, Incyte, Daiichi-Sankyo, Servier, Syndax,Sumitomo and Kura
- IDMC for Takeda, Janssen
- Steering committee for Sumitomo, Kura , Servier and Pfizer

Clonal Hematopoiesis

Clonal hematopoiesis: Age-related expansion of a clonal population of hematopoietic stem or progenitor cells

Somatic Mutations



CHIP = Clonal hematopoiesis of indeterminate potential
- Somatic mutation in **myeloid** malignancy driver gene
- **Variant allele fraction (VAF) ≥ 0.02 (2%)**
- No cytopenias

CCUS = Clonal cytopenia of uncertain significance
- CHIP + unexplained & persistent anemia, thrombocytopenia, or neutropenia

Lymphoid CH (L-CHIP) = CH caused by somatic alterations in lymphoid malignancy driver mutations

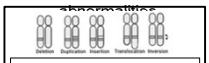
Micro-CH = low abundance clones [VAF < 0.02 (2%)]

Khoury et al. Leukemia. 2022

Unknown drivers (CH-UD)

? **Undetected drivers**
? **Unclassified somatic alterations**
? **epigenetic drivers of clonality**

Mosaic chromosomal

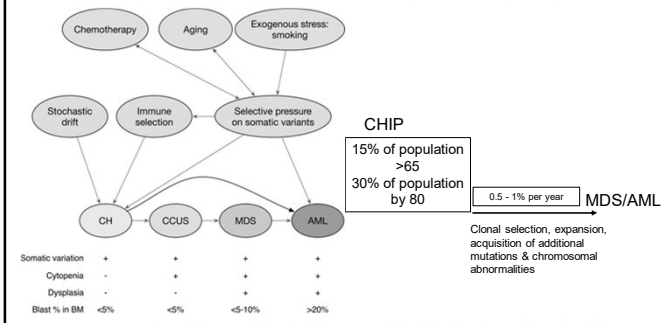


L-mCA = chromosomal alterations associated with lymphoid malignancies

M-mCA= chromosomal alterations associated with myeloid malignancies

Niroula et al. Nature Medicine. 2021

CHIP and CCUS are precursors to myeloid malignancy



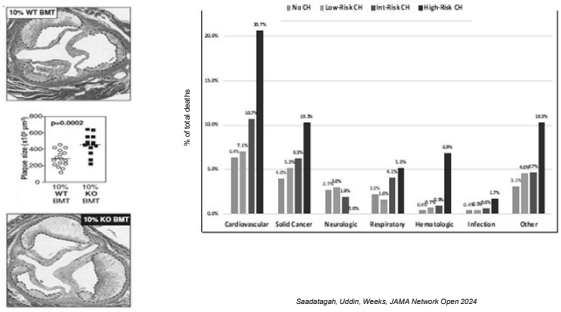
CHIP
15% of population >65
30% of population by 80

0.5 - 1% per year → MDS/AML

Clonal selection, expansion, acquisition of additional mutations & chromosomal abnormalities

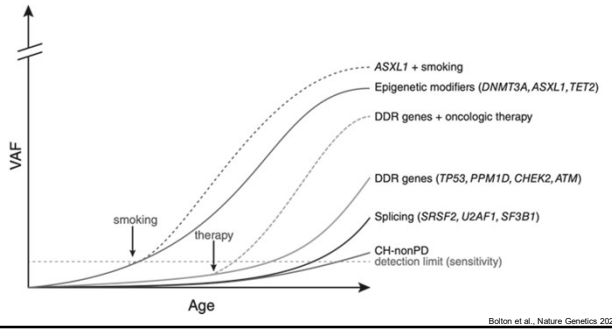
Bowman RL, Busque L, Levine RL. Clonal Hematopoiesis and Evolution to Hematopoietic Malignancies. Cell Stem Cell. 2018 Feb 1;22(2):157-170.

Excess mortality in CHIP/CCUS is driven by non-malignant diseases



Saadatagah, Uddin, Weeks, JAMA Network Open 2024

Context-dependent expansion of CH & myeloid malignancy predisposition



Bolton et al., Nature Genetics 2020

Clinical considerations for CHIP/CCUS detection, risk stratification and intervention

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Incidental Detection of CHIP/CCUS

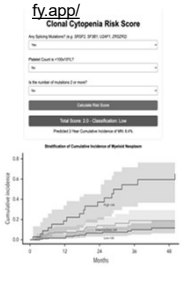
Clinical Considerations

- **CHIP/CCUS is identified in various clinical contexts**
  - Evaluation of abnormal blood counts
  - Hereditary cancer panel testing
  - Solid tumor: tissue and liquid biopsies
  - Patients consented to research screening protocols
- Once a patient knows their CHIP/CCUS status they should have access to counseling regarding the significance of CHIP/CCUS, risk stratification, and risk-specific management

Dr. L Weeks, DFCI, FDA symposium 2026

CH risk calculators available for clinical use

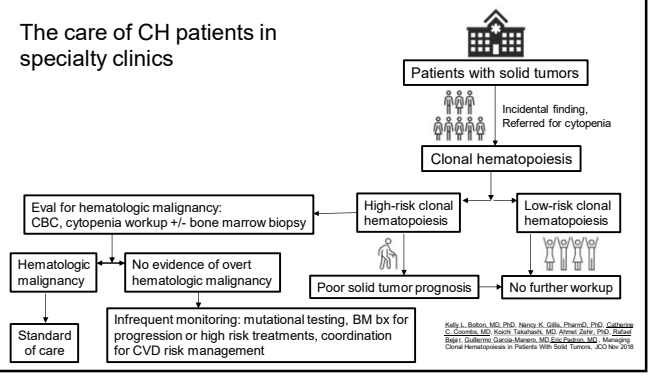
https://ccrscalc.netlify.app/



http://www.chrsap

https://bioinf.stemcells.cam.ac.uk/shiny/vassiliou/MN_predict/

The care of CH patients in specialty clinics



Kelly L. Bolton, MD, PhD, Nancy K. Gillis, PharmD, PhD, Catherine C. Coombs, MD, Kochi Takahashi, MD, Ahmet Zehir, PhD, Rafael Bejar, Guillermo Garcia-Manero, MD, Eric Padron, MD. Managing Clonal Hematopoiesis in Patients With Solid Tumors. JCO Nov 2018

Risk-informed management of CH

All patients

CHRS Risk stratification

	10-year Risk of Myeloid Malignancy	Malignancy Risk Mitigation Strategy
High risk (1%)	>50%	• Q3-6mo CBC • Repeat NGS annually • Repeat bone marrow with clinical changes • Consider risk/benefits of clinical trials
Intermediate risk (10%)	7-8%	• Annual CBC • Repeat NGS with clinical change • Repeat bone marrow with clinical changes
Low risk (89%)	<1%	• Annual CBC • Repeat NGS with clinical change • Repeat bone marrow with clinical changes

Lachelle D. Weeks,Benjamin L. Ebert, Causes and consequences of clonal hematopoiesis, Blood, 2023

Weeks and Ebert. Blood. 2024

"Diagnosis" with CH could harm

Table 5. **Participants' perceived concerns and benefits regarding CHIP testing**

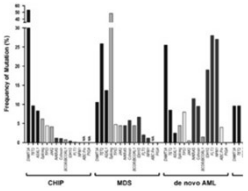
	Strongly disagree n (%)	Somewhat disagree n (%)	Neither agree nor disagree n (%)	Somewhat agree n (%)	Strongly agree n (%)	
Finding out that I had CHIP would be more than I could handle emotionally	124 (23.5)	114 (21.6)	137 (25.9)	93 (17.6)	27 (5.1)	Emotional harm
This information about one's future health risks is better left unknown	237 (44.9)	120 (22.7)	73 (13.8)	43 (8.1)	23 (4.4)	Decisional regret
I am concerned about the test because it is new and hasn't been used widely	89 (16.9)	110 (20.8)	164 (31.1)	113 (21.4)	19 (3.6)	
I am concerned that the test being so new prevents me from asking other patients about their experiences with it	154 (29.2)	96 (18.2)	136 (25.8)	92 (17.4)	15 (2.8)	
The results will help me change my behaviors and reduce my disease risk	15 (2.8)	28 (5.3)	77 (14.6)	231 (43.7)	143 (27.1)	Overmedicalization
The results will help me seek medical attention and reduce my disease risk	9 (1.7)	17 (3.2)	62 (11.7)	230 (43.6)	177 (33.5)	
I am concerned I could lose my job/insurance if the results get out	304 (38.6)	91 (17.2)	104 (19.7)	71 (13.4)	26 (4.9)	
I am concerned about costs related to CHIP testing or recommended follow-up	95 (18.0)	57 (10.8)	104 (19.7)	149 (28.2)	91 (17.2)	Financial toxicity
I may learn that I have an increased risk for a disease that I did not want to know about	150 (28.4)	92 (17.4)	89 (16.9)	121 (22.9)	45 (8.5)	
I may learn that I have a condition that I can do nothing about	68 (12.9)	62 (11.7)	78 (14.8)	203 (38.4)	85 (16.1)	No interventions

Courtesy L Weeks, FDA symposium 2026

Seifa T. Blood Advances. 2022

Should we intervene early and intercept high risk CH(CCUS) ?

- Fact: CH mutations can be detected and precede MDS /CMML/ AML development by many years.
- *Clinical implication: Window for early intervention ?*
- Fact: We know certain high risk CH mutations are found in dominant clones of MDS and AML patients
- *Clinical implications: Can we target these mutations and/or other stressors that lead to clonal expansion to prevent disease progression ?*
- Can we define a high-risk CH population where early intervention is justified based on risk vs benefit calculation with the appropriate clinically meaningful endpoints ?



- **Personalized risk prediction:** identifying individuals/patients at highest risk of progression to a myeloid neoplasm
- **Tolerable therapeutic interventions:** treating individuals/patients with agents that match their risk profile

BJHaem

REVIEW | Open Access

A blueprint for pursuing therapeutic interventions and early phase clinical trials in clonal haematopoiesis

Tamanna Haque, Aditi Shastri, Pinkal Desai, Zhuoer Xie, Danielle Hammond, Zoe King, Ashwin Kishtagari, Yazan F. Madanat, Yasmin Abaza, Alexander J. Silver, Abhay Singh, Uma M. Borate, J. Brett Heimlich, David A. Slosky, Kelly L. Bolton, Mrinal S. Patnaik, Alexander G. Bick, Amit K. Verma, Siddhartha Jaiswal, David P. Steensma, Michael R. Savona ... See fewer authors

First published: 09 December 2024 | https://doi.org/10.1111/bjh.19925 | Citations: 3

Tamanna Haque and Aditi Shastri contributed equally to this study.

Current active CHIP/CCUS clinical trials

Slide courtesy of Dr. Chien

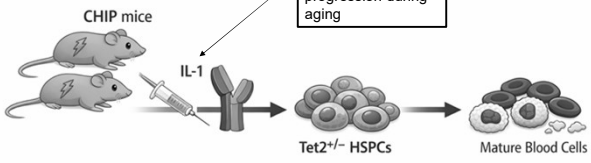
Agent	Conditions	Included Mutations	Cytopenia Definition	Goal Enrollment	Active Malignancy Allowed	Primary Endpoint	Length of Therapy	NCT Number
Enasidenib	CCUS	*IDH2*	Hgb < 10, ANC < 1.8, plt < 100	15-20	6+ mos, no tx	HI (IWG 2006)	18 mos	NCT05102370
Ivosidenib	CCUS	*IDH1*	Hgb < 10, ANC < 1.8, plt < 100	15-20	6+ mos, no tx	HI (IWG 2006)	17 mos	NCT05030441
Olutasidenib	CCUS, LR-MDS/CMML	*IDH1*	WHO criteria	15	Yes	HI (IWG 2018)	18 mos	NCT06566742
Decitabine/ cedazuridine	CCUS (CHRS high-risk)	Any myeloid mutation	WHO criteria	138	Yes if no tx	Safety and feasibility	12 mos	NCT06802146
Atorvastatin or rosuvastatin	CCUS, LR-MDS	Any myeloid mutation	Hgb < 11.3 (F) or < 13 (M), ANC < 1.8, plt < 150	16	2+ yrs, no tx	Δ hs-CRP	12 mos	NCT05483010
Luspatercept	CCUS	Any myeloid mutation	Hgb < 10, ANC < 0.75, plt < 50	50	Yes if no tx	HI (IWG 2018)	Indefinite	NCT06788691
Canakinumab	CCUS [vs placebo]	Splicing mutations at any VAF, TP53 at VAF > 0.05, DTA and/or other CH-associated mutations in combination or at VAF > 0.1	Hgb < 11, 0.5 < ANC < 1.8, 50 < plt < 150	110	Yes if no tx	Time to MN transformation	2 yrs	NCT05641831
	CCUS, LR-MDS	Any myeloid mutation	WHO criteria	70	2+ yrs	HI (IWG 2006), safety	Indefinite	NCT04239157
Curcumin	CCUS, LR-MDS, MPN [vs placebo]	Any myeloid mutation	Hgb < 11.3 (F) or < 13 (M), ANC < 1.8, plt < 150	30	Yes if no tx except hormonal/growth factors	Δ IL-1β, IL-6, IL-18, TGFβ, TNFα levels; QoL	12 mos	NCT06063486
Ascorbic Acid	CCUS [IV]	*TET2*	Hgb < 10, ANC < 1.0, plt < 100	Terminated at 10/55	Yes if no tx except hormonal	HI (IWG 2018)	3 mos	NCT03418038
	CCUS, LR-MDS, CMML-0/1 [PO, vs placebo]	Any myeloid mutation	Hgb < 11.3 (F) or < 13 (M), ANC < 1.8, plt < 150	109	5+ yrs	Δ VAF and median number of mutations	12 mos	NCT03682029
Metformin	CCUS, LR-MDS	Any myeloid mutation	Hgb < 11.3 (F) or < 13 (M), ANC < 1.8, plt < 150	40	Yes if 6+ mos no tx	Safety and feasibility	12 mos	NCT04741945
DFV890 + MAS825	CHIP + h/o MI	*DNMT3A* or *TET2*	No cytopenia allowed	Completed (31)	No	Δ IL-6, IL-18 levels	3 mos	NCT06097663

Adapted from Chien KS et al., *Clin Adv Hematol Oncol* 2024.

IL-1b and CH progression

Aging drives Tet2$^{+/-}$ clonal hematopoiesis via IL-1 signaling

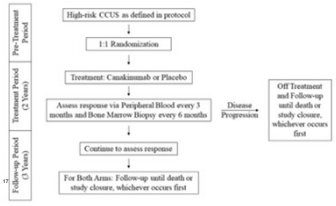
The IL-1 pathway is a relevant and therapeutically targetable driver of *Tet2*$^{+/-}$ CHIP progression during aging



Francisco Caiado,Larisa V. Kovtonyuk,Nagihan G. Gonullu,Jonas Fullin,Steffen Boettcher,Markus G. Manz, Aging drives Tet2+/– clonal hematopoiesis via IL-1 signaling, Blood, 2023,

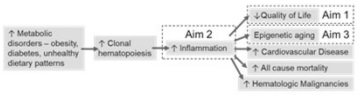
A Randomized Double-Blind Placebo-Controlled Phase II Multi-Center Study of Inflammation Modification of Canakinumab to Prevent Leukemic Progression of Clonal Cytopenias of Unknown Significance (CCUS): IMPACT Study(NCT05641831)

Sample size=70



- OSU: Main site, Cornell, Vanderbilt, UTSW , U Miami & MSKCC: Active, enrolling
- No of patients consented =40
- Screened failed: 18
- Common reasons: already have MDS, don't
- have high enough VAF or correct no/
- combination of mutations,
- 33 patients enrolled
- 3 off study due to other medical reasons not related to study Rx
- (relocation, secondary malignancy)
- 3 off study in follow up after progression to MDS/CMML

Study Design



- Clonal hematopoiesis
- BMI >25 kg/m²
- N=25
- Decentralized trial
- PI: Urvi A. Shah, MD
- Primary site Memorial Sloan Kettering Cancer Center
- Collaborating sites – Mayo (Mrinal Patnaik), Montefiore (Aditi Shastri), Ohio State (Uma Borate)
- To open in Q4 2025
- Primary objective: Quality of life

@UrviShahMD

HALT Program

Hematologic Abnormalities at risk of Leukemic Transformation

PURPOSE: Identify, surveil, and treat *individuals and families* with **hereditary*** or **acquired**† genetic variation, who are at risk of developing, or have already developed, hematologic malignancy

Collaboration with Cardio-Oncology in relevant patients

†Acquired indications:
- Patients with prior chemo exposure and new onset of cytopenias(HR-CCUS)
- Persistent cytopenias with clonal hematopoiesis (CCUS)
- Clonal hematopoiesis of undetermined significance (CHIP)

*Hereditary indications:
- Family history of thrombocytopenia or hem malignancy
- Young adults with monosomy 7
- Clinically suspected genetic predisposition syndrome
- Young-onset (<50y) AML or MDS
- Sibling HSCT candidate donors of suspected patient
- Potentially germline pathogenic variant found on somatic panel

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Conclusions and Summary

- Presence of CH has multiple implications for both non-oncologic and oncologic diseases and adverse outcomes
- Appears to be the ubiquitous villainous side kick, makes bad things worse by facilitating inflammatory pathways and immune response disruption
- The subsets of people/patients at high risk for adverse outcomes are increasingly being able to be identified
- Multiple efforts ongoing to find the right interventions-medications and lifestyle.

Where the field is going

- Figure out the best endpoints that are meaningful to patients
- Identify intervention(s) that prioritizes patient safety with prolonged exposure
- Patient selection
  - TP53 mutated CCUS
  - Therapy emergent CCUS
- -post curative solid tumor therapy
- -post CAR-T
- -post MM maintenance therapy
- Sickle cell gene therapy ?

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Monoclonal B Lymphocytosis (MBL)

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Objectives

- To understand the definition and natural history of MBL
- To understand the clinical consequences of MBL

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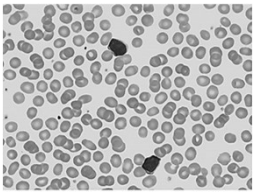
What is Monoclonal B Lymphocytosis (MBL)?

- Accumulation of clonal B cells with a phenotype similar to:
  - CLL (CD5+/CD20dim/CD19+/CD23+)
  - Atypical CLL (CD20 mod/bright and/or CD23-)
  - Non-CLL (CD5 neg)
- Monoclonal B cells must persist for at least 3 months
- CLL is always preceded by MBL, but MBL does not always lead to CLL



Rawstron et al, Blood 2002

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Differentiating MBL from CLL/SLL

Diagnosis	CLL Clone ≥5k	Enlarged Lymph Nodes	Enlarged Liver or Spleen	Cytopenias due to Marrow Infiltration
CLL	Required	+/-	+/-	+/-
SLL	-	Required	+/-	-
MBL	-	-	-	-

MBL = Monoclonal B-Lymphocytosis, SLL = Small Lymphocytic Lymphoma

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What is Monoclonal B Lymphocytosis (MBL)?

- Prevalence of MBL 3.5-12% over age 40
- Variance due to test sensitivity
- High count (HC) MBL is 500-5000 clonal B cells/μL, Low count (LC) is <500 clonal B cells/μL
- Population based screening will detect mostly low count MBL which is otherwise not clinically apparent

Age	Risk of MBL
40-49	4%
60-69	16%
80-89	28%
90+	42%

Rawstron et al, Blood 2002, Slager et al, Blood 2021, 2022

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Natural History of CLL-like MBL

- Low count MBL is often found only on population based screening, or flow cytometry performed for a different reason. Except in familial cases, progression to CLL is rare
- High count MBL advances to CLL requiring therapy at a rate of 1%/year

Rawstron et al, NEJM 2008

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Natural History of CLL-like MBL

- Population based study of >10,000 individuals
- Incidence of MBL increased with age
- Persons with MBL had 7.7-fold increased risk of lymphoid malignancies
  - 74-fold for HC
  - 4.3-fold for LC
- No difference in survival

Slager et al, Blood 2022

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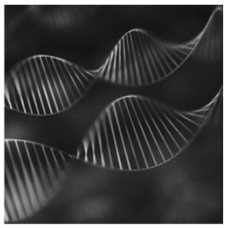
Genomic alterations in MBL

- Population-based study of 4632 individuals: 2971 without MBL/CLL, 728 LC-MBL, 332 HC-MBL, 497 CLL, 104 SLL
- By SNP array, recurrent CLL-associated abnormalities common in HC-MBL (52.1%), rare in LC-MBL (1.1%)
- Del11q/del17p lower in MBL than CLL



Sekar et al, Blood Cancer J 2024

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Complications of MBL: Infections

- Population study using Mayo biobank
- 1045 individuals screened, 12% had MBL (11% CLL-like)
- Incidence of any infection, pneumonia, sepsis higher in MBL vs controls (HR 1.68)

↑ Increased risk of infections

Shanafelt et al, Leukemia 2021

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Complications of MBL: Infections

- Case control study of MBL vs CLL vs neither
- Risk of hospitalization due to infection was similar for MBL (HR 3.0) and CLL (HR 3.2) vs controls
- IGG levels or T/NK cell count not different between MBL and controls
- COVID19 requiring hospitalization higher in MBL (primarily LC) HR 3.29

Moreira et al, Leukemia 2013, Parikh et al, Blood Cancer J 2022

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Complications of MBL: Secondary Cancers

- Case control study of MBL vs CLL vs neither
- Median follow-up about 4.5 years
- CLL and MBL patients had higher rates of hematologic and non-hematologic cancers than controls.
- Secondary cancers of higher proportion in MBL included breast, lung, GI tract, CNS

↑ Increased risk of cancer

Solomon et al, Leukemia 2016

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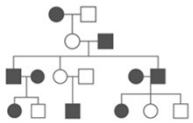
Familial MBL

- CLL has a strong familial component, with first-degree relatives of CLL patients having 8.5 fold increased risk of CLL
- From 310 CLL families, 22% of >1000 individuals were found to have MBL at screening (mostly LC CLL-like)
- With median f/u of 8.1 years:
  - 5-year CI of CLL was 1.8%
  - 5-year CI of CLL from LC-MBL was 5.7% (1.1%/year)



Slager et al, Blood 2021

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Recommended workup for MBL

- History including family history and exposures
- Physical exam focusing on evidence of infection, inflammation, or other malignancy
- CBC with differential
- Blood smear
- For non-CLL MBL, initial workup should include FISH for t(11;14) and cross-sectional imaging to rule out peripheral blood involvement of NHL

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MBL monitoring

- Low count, non-familial probably does not require routine monitoring by a hematologist
- High count CLL-like MBL, atypical MBL, and non-CLL MBL should be monitored for progression to CLL or other hematologic malignancies with CBC and exam. Every 6 months for first two years, then annually unless progression.

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Take Home Points

- MBL is a pre-malignant condition with clinical consequences
- MBL is commonly seen in older adults, with HC-MBL associated with a risk of progression to CLL
- Families of CLL patients have a particularly high risk of MBL, and LC-MBL has high risk of progression to CLL
- Risk of infection and secondary cancers are higher among persons with MBL, including LC-MBL, and these are higher risk than risk of death from CLL

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Pre-malignancies in hematology: plasma cell disorders

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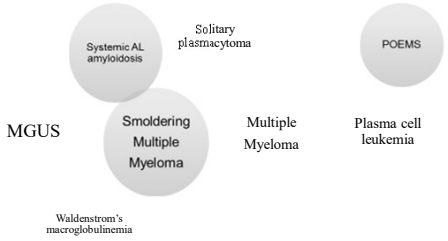
Objectives

- MGUS
- Monoclonal gammopathy of clinical significance
- Smoldering multiple myeloma

Spectrum of plasma cell disorders



Diagnostic criteria for plasma cell disorders

Disorder	*Disease definition*
Monoclonal gammopathy of undetermined significance	All three criteria must be met Serum monoclonal protein <3 gm/dl Clonal bone marrow plasma cells <10%, and Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions that can be attributed to the plasma cell proliferative disorder
Smoldering multiple myeloma (also referred to as asymptomatic multiple myeloma)	Both criteria must be met Serum monoclonal protein (IgG or IgA) ⩾3 gm/dl and/or clonal bone marrow plasma cells ⩾10%, and Absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to a plasma cell proliferative disorder
Multiple myeloma	All three criteria must be met except as noted Clonal bone marrow plasma cells ⩾10% Presence of serum and/or urinary monoclonal protein (except in patients with non-secretory multiple myeloma), and Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically Hypercalcemia: serum calcium ⩾11.5 mg/dl or Renal insufficiency: serum creatinine >1.73 mmol/l) Anemia: normochromic, normocytic with a hemoglobin value of >2 g/dl below the lower limit of normal or a hemoglobin value <10 g/dl Bone lesions: lytic lesions, severe osteopenia or pathological fractures

Work-up in suspected plasma cell disorder

Assessment of serum/urine protein
- SPEP/IF, 24 hr urine for UPEP/IF
- Serum free light chains (kappa, lambda)

CBC,
CMP (Cr, Calcium, Albumin, LDH)
Serum beta 2 macroglobulin (B2M)
Imaging: whole body low dose CT/PETCT, MRI
Bone marrow aspirate and biopsy in certain cases
- Cytogenetics
- FISH myeloma panel

MGUS-diagnosis

Table 1. Criteria for diagnosis and risk of progression in MGUS

Subtype of MGUS	Diagnostic criteria	Risk of progression	Pattern of progression
IgM MGUS	All 3 criteria must be met: • Serum IgM monoclonal protein <3 gm/dL • Bone marrow lymphoplasmacytic infiltration <10%* • No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder	1% per year	Waldenström macroglobulinemia, AL amyloidosis; rarely IgM multiple myeloma
Non-IgM MGUS	All 3 criteria must be met: • Serum monoclonal protein (non-IgM type) <3 gm/dL • Clonal bone marrow plasma cells <10%* • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder	0.5% per year	Multiple myeloma, solitary plasmacytoma, AL amyloidosis
Light-chain MGUS	All criteria must be met: • Abnormal FLC ratio (<0.26 or >1.65) • Increased level of involved light chain (increased κ FLC in patients with FLC ratio >1.65 and increased λ FLC in patients with FLC ratio <0.26) • No immunoglobulin heavy-chain expression on immunofixation • Absence of end-organ damage that can be attributed to the plasma cell proliferative disorder • Clonal bone marrow plasma cells <10%* • Urinary monoclonal protein <500 mg per 24 h	0.3% per year	Light-chain multiple myeloma and AL amyloidosis

Go RS and Rajkumar SV, Blood, 201

MGUS prevalence

Prevalence of MGUS is roughly 1% per year and largely depends on the presence or absence of risk factors.

MGUS – Mayo prognosis and risk assessment tool:

https://qxmd.com/calculate/calculator_148/mgus-prognosis

Questions:

1.M-Protein Size? (< 1.5/> 1.5 g.dl)

2.M-Protein Type? (IgG, IgA, IgM)

3.Serum Free Light Chain Ratio? (normal/abnormal)

MGUS – Need for bone marrow evaluation?

https://istopmm.com/riskmodel/

*The predicted risk of having ≥10% bone marrow plasma cells is **59.6%***

→ Patient had 7% BMPC

Eythorsson E et al., Ann Intern Med, 2024

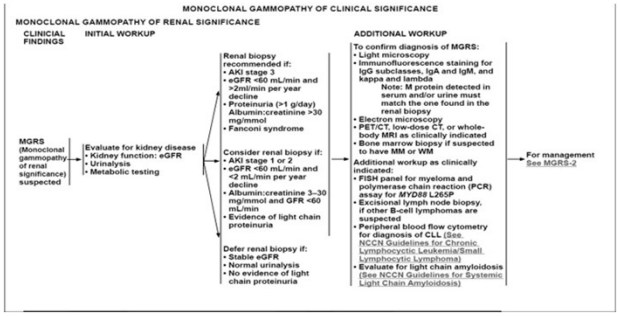
MGUS – follow up

Rx: active surveillance based on the risk factors:
- very low (0 risk factors) – at 6 mo, then every 2-3 years
- low (1 risk factor) – at 6 mo then yearly
- intermediate high (2 risk factors)
- high (3 risk factors)

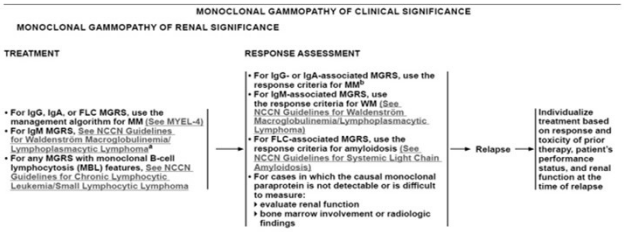
MGCS – monoclonal gammopathy of clinical significance

MGUS + organ effect
- Renal = MGRS
- Neurological =MGNS

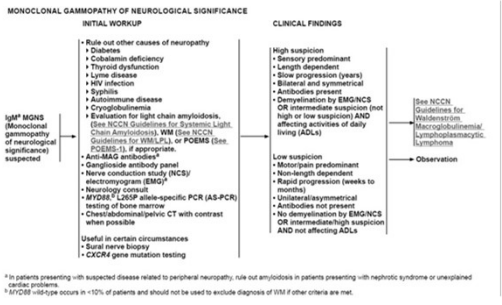
MGRS - NCCN



MGRS - NCCN



MGNS-NCCN



Smoldering multiple myeloma – Diagnosis

DEFINITIONS OF MYELOMA AND RELATED PLASMA-CELL DISORDERS

Disease	Definition
Smoldering Myeloma[a,b] (Asymptomatic)	• Serum monoclonal protein ≥3 g/dL or • Bence-Jones protein ≥500 mg/24 h and/or • Clonal bone marrow plasma cells (BMPCs) 10%–59% and • Absence of myeloma-defining events or amyloidosis
Multiple Myeloma[a,c] (Symptomatic)	• Clonal BMPCs ≥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
Solitary Plasmacytoma[a]	• Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells • Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) • Absence of myeloma defining events • Normal bone marrow with no evidence of clonal plasma cells
Solitary Plasmacytoma with minimal marrow involvement[a]	• Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells • Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) • Absence of myeloma defining events • Clonal bone marrow plasma cells <10%
Plasma Cell Leukemia	• Presence of ≥5% of plasma cells in circulation

[a] Adapted with permission from Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;15:e538–e548.
[b] BMPCs >20%, M-protein >2 g/dL, and FLC r >20 are variables used to risk stratify patients at diagnosis. Patients with two or more of these risk factors are considered to have a high risk of progression to MM. Lakshman A, Rajkumar SV, Buadi FK, et al. Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. Blood Cancer J 2018;8:59.
[c] Other examples of active disease include: repeated infections, amyloidosis, light chain deposition disease, or hyperviscosity.

NCCN Guidelines v2.2026

SMM Mayo 2018 risk stratification

20/2/20

Bone marrow plasma cells >20 percent

M protein >2 g/dL

Involved/uninvolved free light chain (FLC) ratio >20

Risk of progression based on Mayo risk stratification:

High risk (two or three factors present) estimated m TTP- 29 months; estimated risk of progression of 24 percent per year during the first two years, 11 percent per year for the next three years, and 3 percent per year for the next five years.

Intermediate risk (one factor present) – Estimated median TTP 68 months; estimated rate of progression of 15 percent per year during the first two years, 7 percent per year for the next three years, and 4 percent per year for the next five years.

Low risk (no factors present) – Estimated median TTP of 110 months; estimated rate of progression of 5 percent per year during the first 10 years

IMWG risk model for SMM:

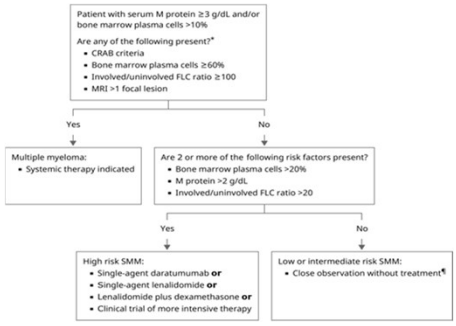
https://qxmd.com/calculate/calculator_847/imwg-risk-model-for-smoldering-multiple-myeloma-smm

Questions:

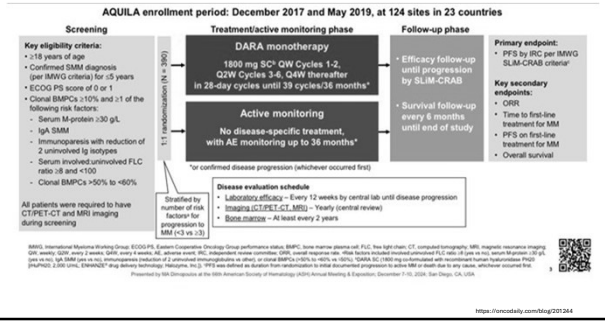
1. The involved to uninvolved free light chain ratio?
2. Serum M-protein level in g/dL?
3. Percentage of bone marrow plasma cell infiltration?
4. Presence of any one of the following cytogenetic abnormalities: t(4;14), t(14;16), +1q, or del13q/monosomy 13?

Calculates total risk score and 2 year progression risk.

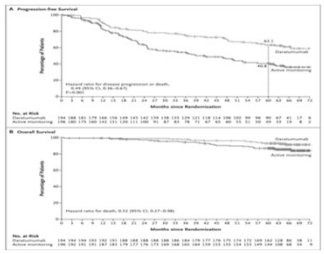
Uptodate SMM management roadmap:



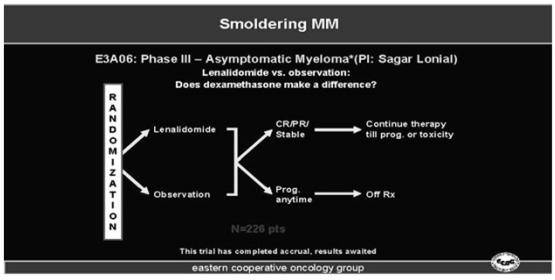
SMM treatment – Aquila trial.



Results:



SMM treatment – ECOG 3A06



Results:

Progression was defined as the development of symptomatic MM as evidenced by biochemical disease progression or related end-organ damage.

Results at 35 mo:

Lenalidomide improved PFS in the entire study population 93% v.s. 76% at two years; HR 0.28, 95% CI 0.12-0.62.

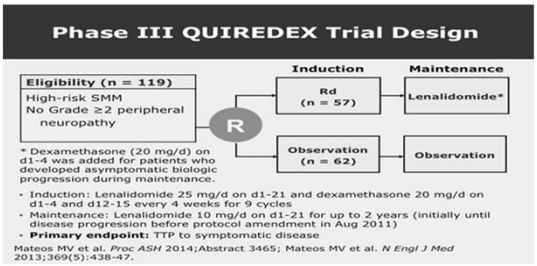
On subgroup analysis, the PFS benefit was clear in patients with high-risk SMM (HR 0.09, 95% CI 0.02-0.44)

Longer follow-up is needed to evaluate OS.

Most toxicities were managed with dose modifications. Approximately 20 percent of patients stopped lenalidomide early due to toxicities.

Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma. AU Lonial S, et all. J Clin Oncol. 2020;38(11):1126. Epub 2019 Oct 25.

SMM treatment – Quiredex



Results

At 75 months:

Improved PFS (median not reached versus 23 months; HR 0.24; 95% CI 0.14-0.41) with fewer patients progressing to MM (39 versus 86 percent).

Improved OS (94 versus 80 percent at three years; HR 0.43; 95% CI 0.20-0.90). Median OS had not been reached in either group.

SMM – Summary

Risk stratification

- Use Mayo 2018/IMWG 20-2-20 criteria

Treatment:

- Low/intermediate-risk
  - Surveillance q3-6m
- High-risk
  - Enroll to clinical trial
  - Daratumumab > lenalidomide +/- dexamethasone