SnapShot: Multiple Myeloma

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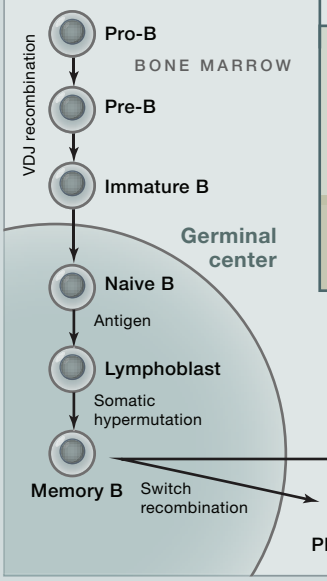
Cancer Cell

Cell of origin



Pathogenesis and disease evolution

Early genetic events

IgH translocations

t(11;14) → *CCND1*
t(4;14) → *WHSC1/FGFR3*
t(14;16) → *MAF*
t(6;14) → *CCND3*
t(14;20) → *MAFB*

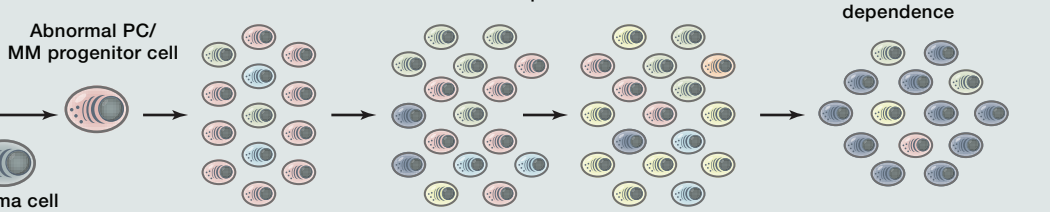
Hyperdiploidy
Trisomies 3, 5, 7, 9, 11, 15, 19, 21

Deletion 13

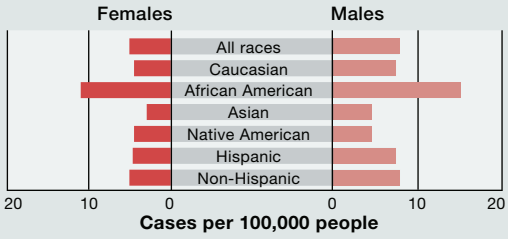
Diagnosis

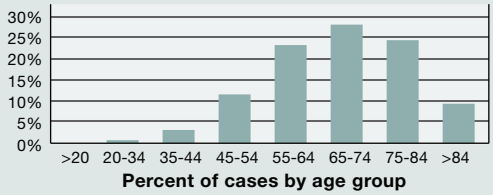
MGUS → SMM → Multiple myeloma → Extramedullary MM/PCL

MAPK mutations
NF-κB mutations
MYC rearrangements
TP53 mutations
Genomic heterogeneity



Epidemiology



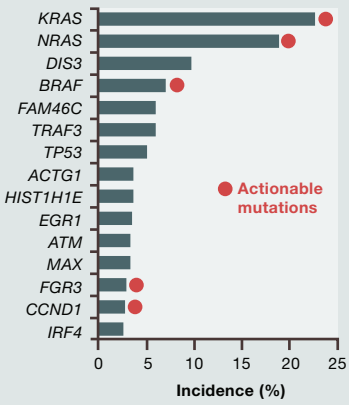


Risk stratification

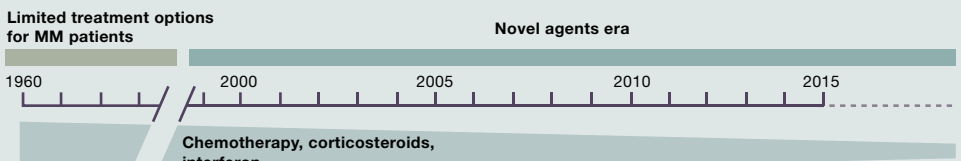
mSMART

High risk	Intermediate risk	Standard risk
FISH Del(17p) t(14;16) t(14;20)	**FISH** t(4;14) 1q gain	**All others, including:** Trisomies t(11;14) t(6;14)
GEP High risk signature	**Complex karyotype** **Metaphase deletion 13 or hypodiploidy** **High PC S-phase**	

Recurrently mutated genes in untreated MM

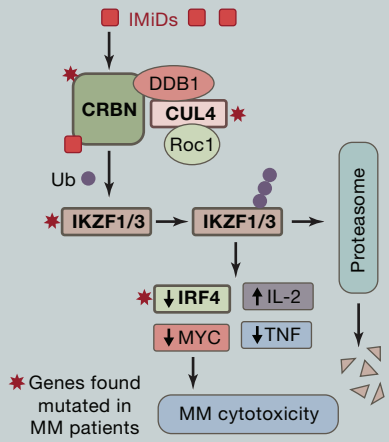


Treatment and survival



Year	1975	1980	1985	1990	1999	2003	2007
5-year relative survival	26.6%	25.8%	27.0%	29.7%	33.5%	41.8%	45.1%
Increase to 1975	-	-3%	2%	12%	26%	57%	70%

Mechanism of action: IMiDs



See online version for legend and references.

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Cancer Cell

Cell of Origin and Epidemiology

Multiple myeloma (MM) is a hematological malignancy characterized by abnormal accumulation of clonal plasma cells (PCs) in the bone marrow (BM). MM accounts for 10% of hematological malignancies and 1.6% of all U.S. cancer deaths. The median age at diagnosis is 69. Significant prevalence differences are observed between age, gender, and race, suggesting a genetic predisposition to MM. In most cases, MM is preceded by a pre-malignant condition, monoclonal gammopathy of undetermined significance (MGUS), followed by an asymptomatic phase, called smoldering myeloma (SMM). The risk of progression to MM is estimated 0.5%–1% per year for the heavy chain and 0.3% for the light chain MGUS.

Diagnosis and Clinical Presentation

The presence of a serum monoclonal protein <30 g/L, clonal BM PCs <10%, and absence of disease-related end-organ damage including calcium elevation, renal insufficiency, anemia, and bone disease ("CRAB criteria") defines MGUS. Increased number of BM PCs (10%–60%) or serum/urinary monoclonal protein exceeding MGUS limits defines the transition to SMM. MM is defined by BM PCs >10% and the presence of CRAB criteria. Patients require MM therapy regardless of the presence of CRAB criteria if BM PC ≥ 60%, the involved/uninvolved serum free light chain ratio is > 100, or focal BM lesions are identified by MRI. Increased osteoclastic and decreased osteoblastic activity is commonly present in MM leading to secondary hypercalcemia, generalized osteopenia, focal osteolytic lesions, and pathological fractures.

Genomic Abnormalities

Genetic aberrations are observed from the early stages of the disease and are key events in the establishment of the clonal PC population. The clonal architecture of MM is characterized by multiple independent, yet related, clones at diagnosis with shifting predominance during progression that is particularly affected by therapy. MM can be classified into two major subtypes: hyperdiploid MM (H-MM) and non-hyperdiploid MM (NH-MM). Each group comprises approximately half of patients with very low overlap. H-MM exhibits non-random extra copies of multiple chromosomes, especially chromosomes 3, 5, 7, 9, 11, 15, 19, and 21. The NH-MM is mainly characterized by IgH translocations, leading to the activation of proto-oncogenes located in multiple partner chromosomes such as 11p13 (*CCND1*; found in ~18% of patients), 4p16 (*MMSET* and *FGFR3*; ~15%), 16q23 (*MAF*; ~4%), 6p21 (*CCND3*; ~1%), and 20q12 (*MAFB*; ~1%). Each of these translocations is associated with a specific prognostic outcome.

Nearly half of MM patients have mutations in the MAPK pathway, including *KRAS* (~23%), *NRAS* (~19%), and *BRAF* (~7%). Putative MM genes include *DIS3* and *FAM46C*, mutated in 10% and 7%, respectively. Recurrent mutations are also found in genes of the NF-κB signaling pathway (*TRAF3*, *CYLD*), cell cycle (*CCND1*, *RB1*), and DNA damage response (*ATM*, *TP53*). The mutation incidence increases with disease progression, especially in *TP53*, which is mutated in most cases of PC leukemia. *MYC* dysregulation is found in nearly one-third of patients through chromosomal translocations, insertions, deletions, and inversions. Actionable mutations are recurrently found in *KRAS*, *NRAS*, *BRAF*, *FGFR3*, *CCND1*, *IDH1*, and *IDH2*.

Relevant Abnormalities in Disease Prognosis and Risk Stratification

Deletion of 17p is a rare event at diagnosis (~10%) but becomes more common with progression. This abnormality is currently the single most important genetic prognostic factor in MM, irrespective of treatment, suggesting that none of the therapies have a significant impact in patients with 17p13 deletion. The gene responsible has not been completely identified, but evidence indicates *TP53* as the strongest candidate. t(14;16)(q32;q23) and t(14;20)(q32;q12) are associated with aggressive disease and a negative outcome in MM treated with conventional, alkylator-based and high-dose chemotherapy. t(4;14)(p16;q32) is associated with intermediate outcome and aggressive clinical features, both at diagnosis and after either standard or high-dose chemotherapy. Bortezomib partially overcomes the negative prognostic effect of t(4;14)(p16;q32). Unbalanced translocations with loss of the der14 (*FGFR3*) are commonly observed, suggesting that *MMSET*, and not *FGFR3*, may play a critical role in the clonal expansion of t(4;14)(p16.3;q32) MM cells. 1q21 gain is seen in one-third of MM cases and has been associated with intermediate risk. The proposed target of this region is *CKS1B*. t(11;14)(q13;q32) is associated with low PC proliferation, low levels of serum monoclonal proteins, and good prognosis.

Hypodiploidy is associated with intermediate risk, whereas H-MM is associated with good prognosis.

Several gene expression profiling (GEP) indices have been implemented in MM to perform risk stratification. Gene sets between 15 and 70 probes, mostly enriched on proliferation genes, are currently used to identify the 15%–20% of newly diagnosed patients with a very poor prognosis.

Recent data suggest that *MYC* translocations and mutations in *TP53*, *CCND1*, *ATM*, *ATR*, and *ZFHX4* had a negative impact in MM. Conversely, mutations in *IRF4* and *EGR1* showed a positive impact on survival.

Prognosis

Risk stratification is mainly based on the existence of genetic alterations and clinical parameters including serum albumin, beta-2 microglobulin level (international staging system), LDH, and PC proliferation rate. Presence of extramedullary disease, high tumor burden, preexisting comorbidities, age, and compromised organ function are further prognostic markers.

Treatment

The era of novel drugs revolutionized MM treatment, including immunomodulatory drugs (IMiDs; Thalidomide, Lenalidomide, Pomalidomide) and proteasome inhibitors (Bortezomib, Carfilzomib) as the main representatives. The mechanisms of action of IMiDs have been recently elucidated, identifying the molecule recognized by the drug (CRBN) as well as key downstream biological effects. A remarkable number of additional drugs either were recently introduced in the clinic (HDAC inhibitor Panobinostat) or are under investigation (monoclonal antibodies, immunotherapies, and other targeted therapies).

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