Infecciones Asociadas a Nuevos Tratamientos para Mieloma Múltiple y Leucemia Linfática Crónica

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Transparency Disclosure

- Research grant
  - Pfizer
- Consulting
  - Pfizer, Merck, Astellas, Gilead, Basilea
- Speaker
  - Pfizer, Merck, Gilead, Astellas, United Medical, Teva

What is in Common Between Myeloma and Chronic Lymphoid Leukemia?

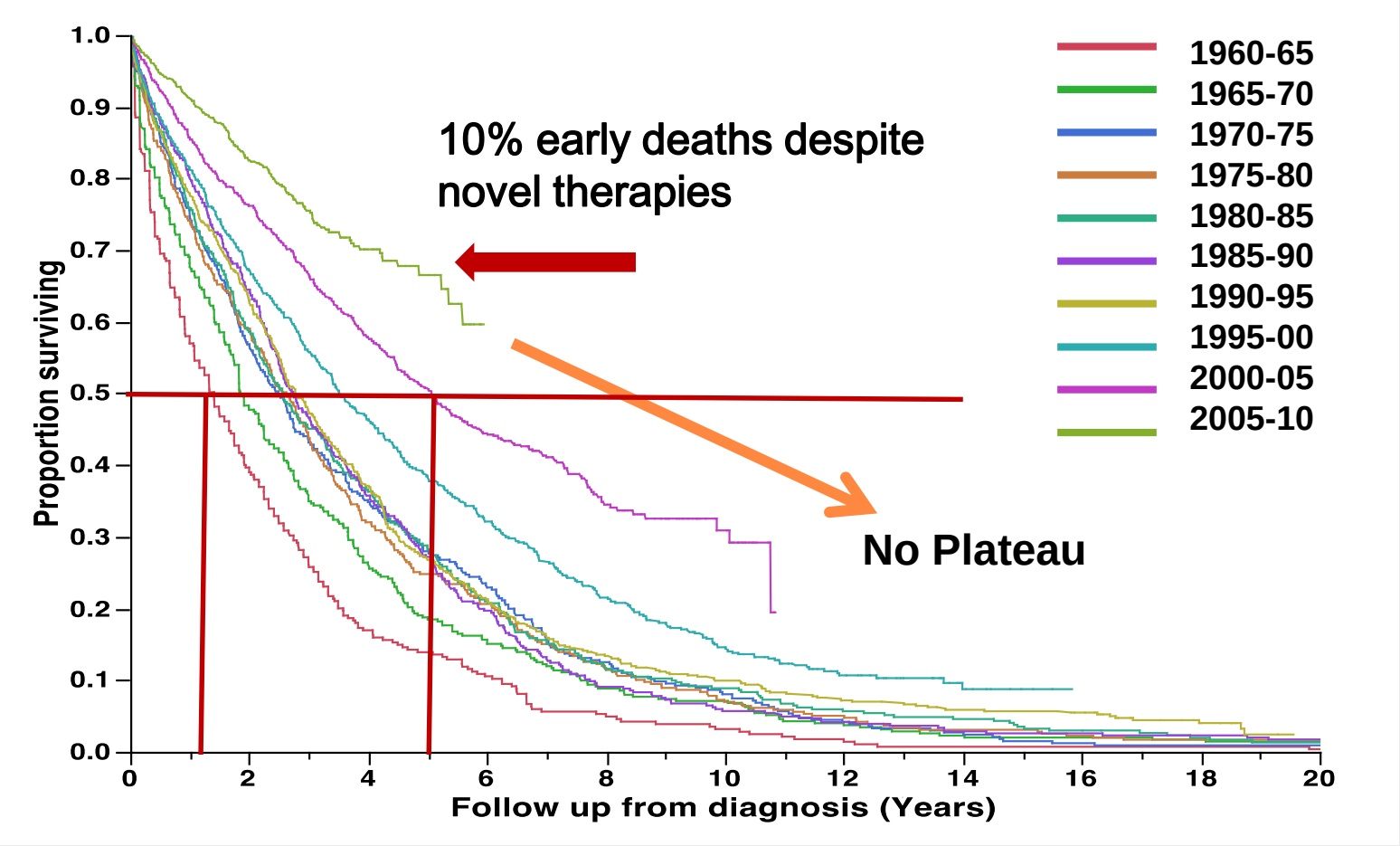
- Chronic lymphoproliferative diseases affecting B lymphocytes
  - Hypogammaglobulinemia
- Prolonged treatment resulting in cumulative immunosuppression
- New drugs recently approved for treatment
  - Myeloma: 6
  - CLL: 5
- Little information on risks and infectious complications

Myeloma and Infection: Population-based Study on 9253 Patients

- All MM patients diagnosed in Sweden 2004-2007; 34,931 controls
- MM patients
  - Risk 7x higher for all infections
    - 11x higher in the 1st year from diagnosis
    - Meningitis, septicemia, pneumonia, osteomyelitis, cellulitis, pyelonephritis
  - Viral: 10x higher (18x 1st year)
    - Influenza, VZV
- After 1 year infection was the underlying cause of death in 22%

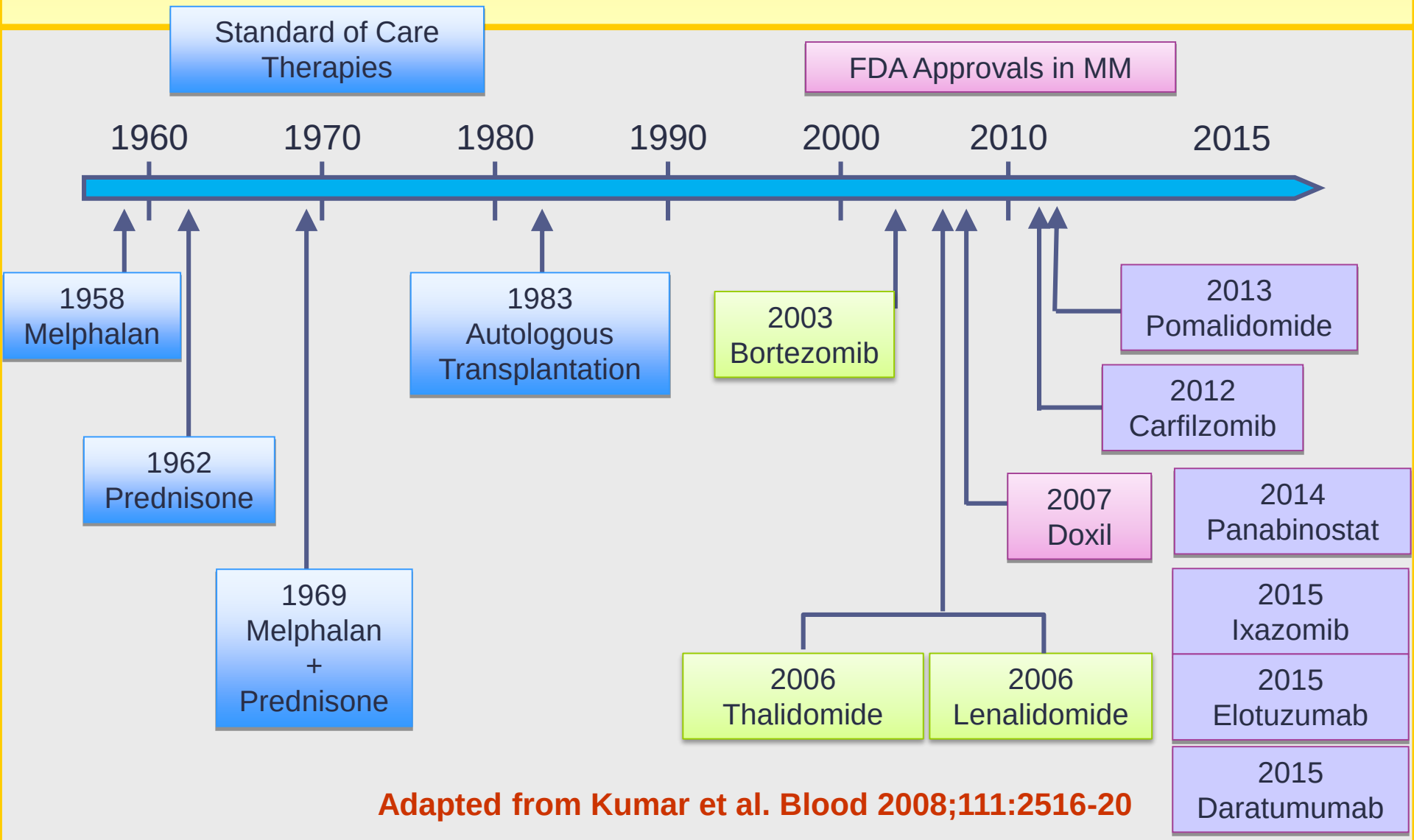
Blimark et al. Haematologica 2015;100:107-13

The Survival of`Patients with Myeloma has Increased Substantially in the Past Decades



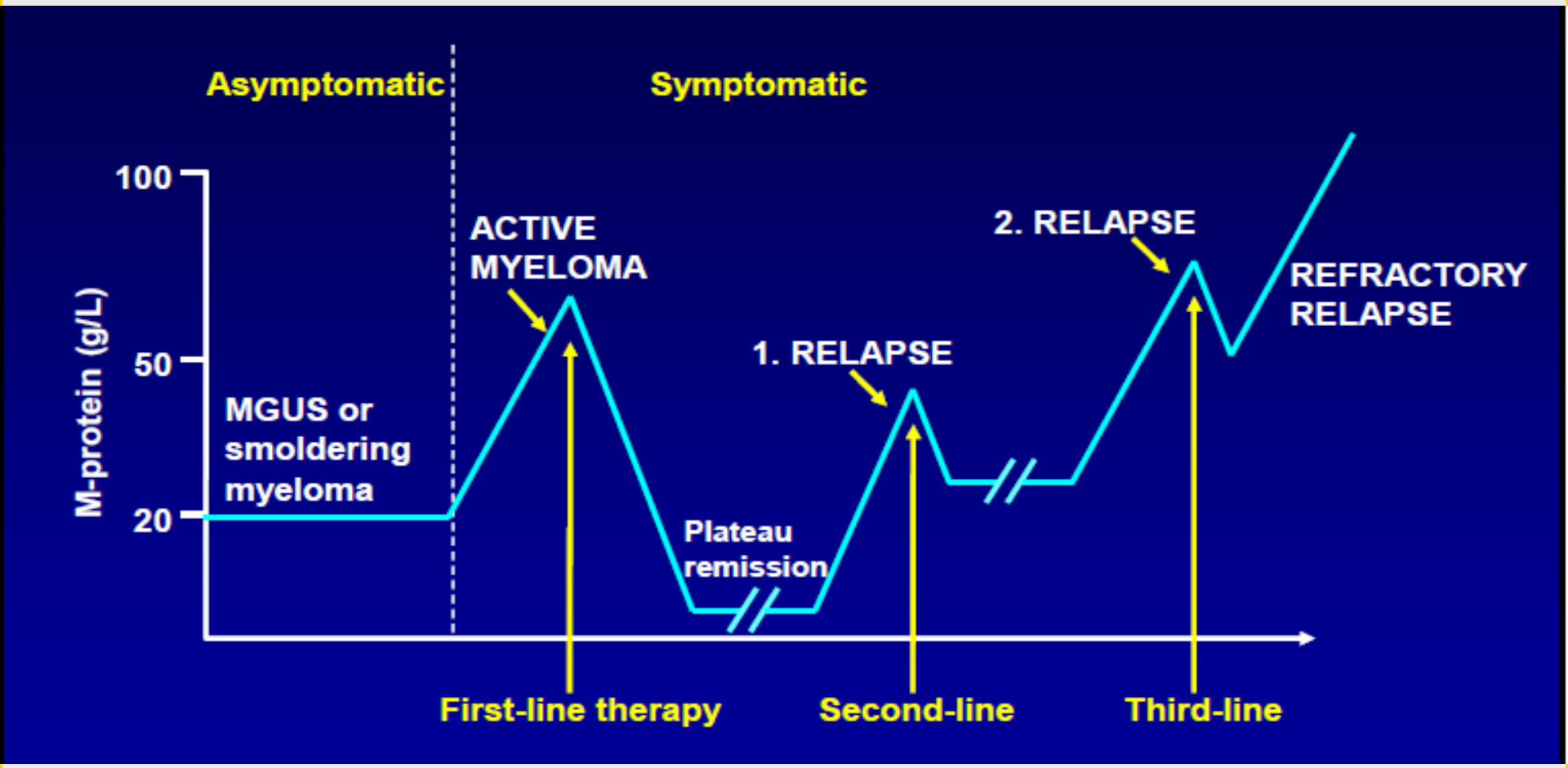
Kumar et al. Leukemia 2014;28:1122-8

Therapy for Multiple Myeloma

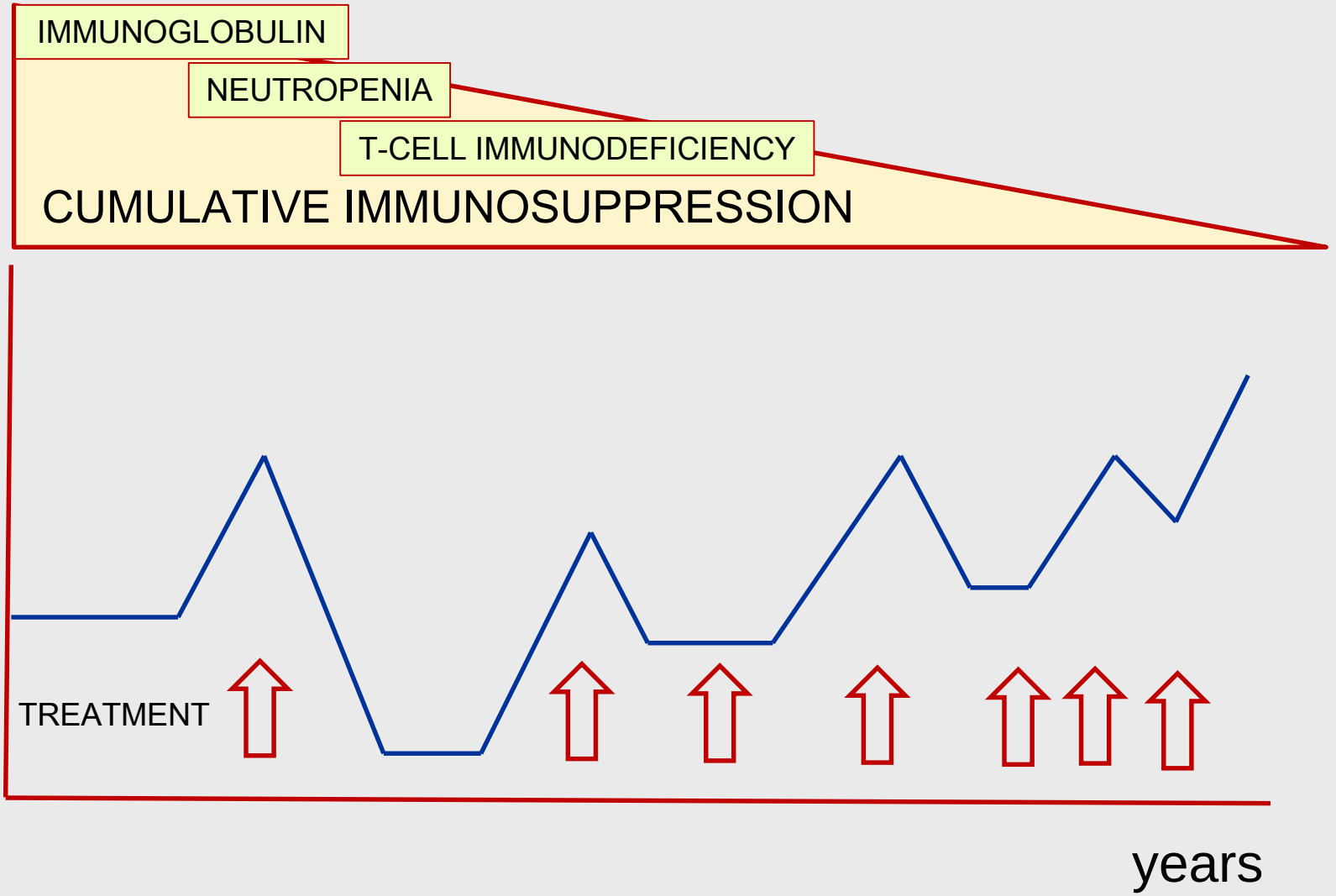


Adapted from Kumar et al. Blood 2008;111:2516-20

Natural History of Multiple Myeloma



Evolution of the Treatment of Myeloma and Immune Status of the Host

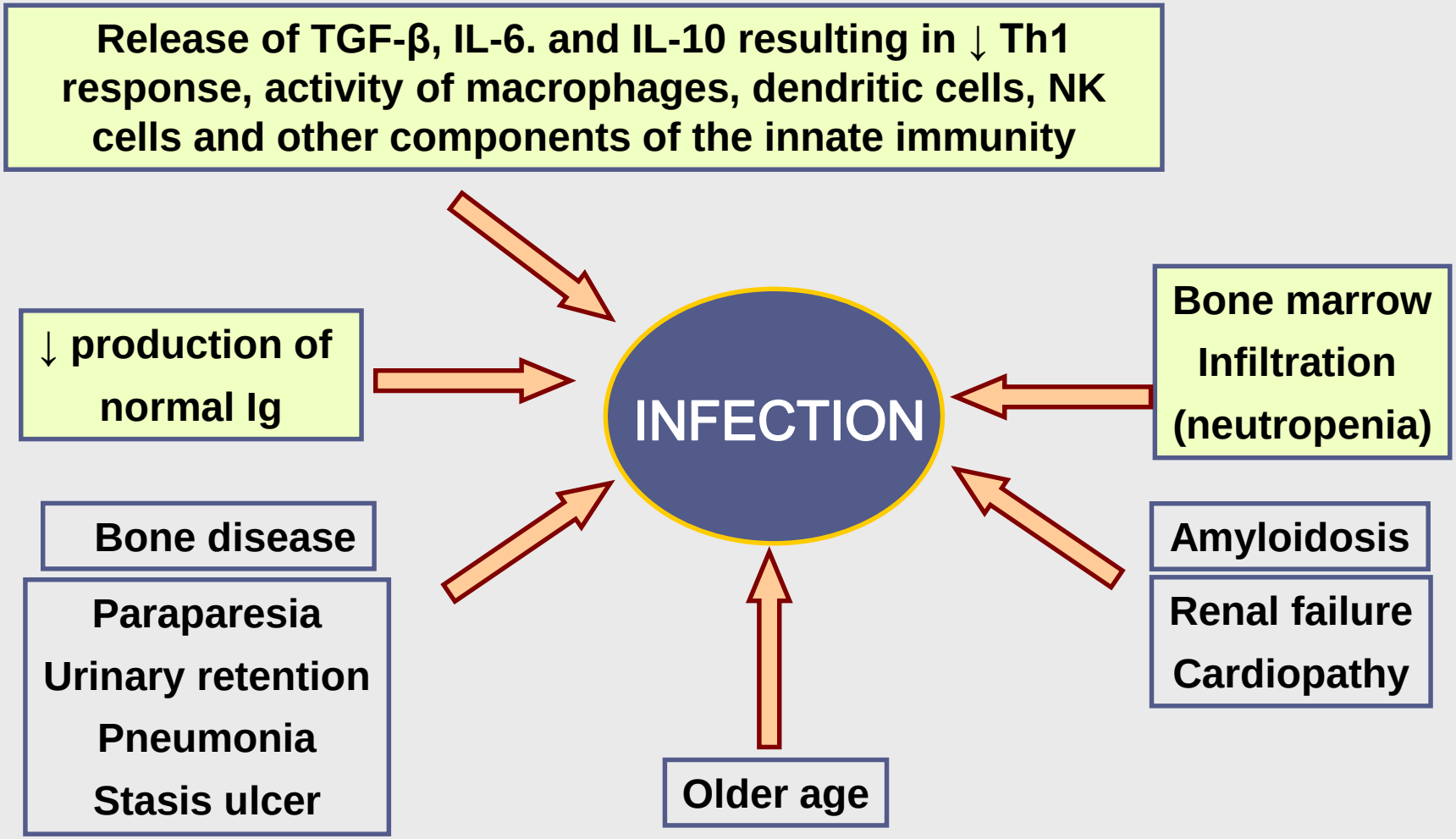


Challenges in Managing Infection in Multiple Myeloma

- New drugs with different mechanisms of action
- Little information about effects of these drugs (alone or in combination) on the normal host defenses
- Control of the disease is achieved thanks to continuous treatment with different drugs and regimens
- Consequence: cumulative immunosuppression

Nucci & Anaissie. Clin Infect Dis 2009;49:1211-25

The Immune System in Untreated Patients with Multiple Myeloma



Tete et al. Front Immunol 2014;5:1-14

Pattern of Infection in the First Months after Diagnosis of Myeloma

- Low levels of normal immunoglobulins in the serum correlate with infection
- Biphasic pattern
  - Encapsulated early
  - Gram-negative and *S aureus* after treatment initiation
- Higher rates of infection in the 1st 2 months after diagnosis, with significant (~10%) mortality
- Higher rates of infection with active disease

Nucci & Anaissie. Clin Infect Dis 2009;49:1211-25

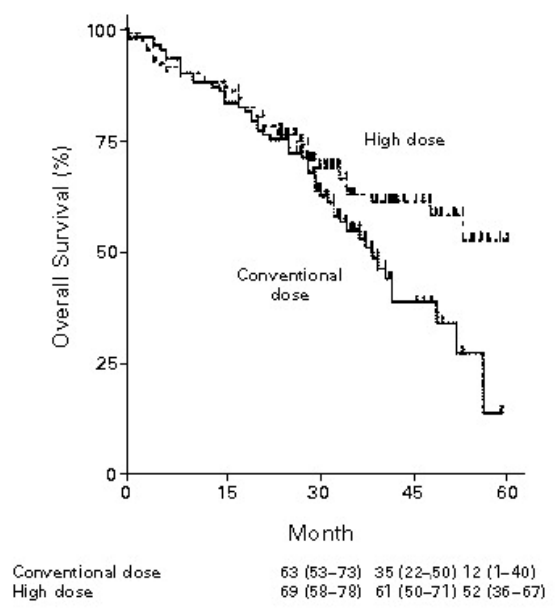
Major Advances in the Treatment of Myeloma in the 1980s and 1990s

Doc, I'm always on Dex

- High-dose dexamethasone
  - salvage of melphalan + prednisone
  - Primary therapy (VAD)
- Regimen: 40 mg/d x 4d x 3 cycles
- CONSEQUENCE: severe T-cell immunodeficiency
  - Broader spetrum of infections, including mucosal candidiasis, herpes simplex, herpes zoster, *Pneumocystis* pneumonia

Nucci & Anaissie. Clin Infect Dis 2009;49:1211-25

Major Advances in the Treatment of Myeloma in the 1980s and 1990s

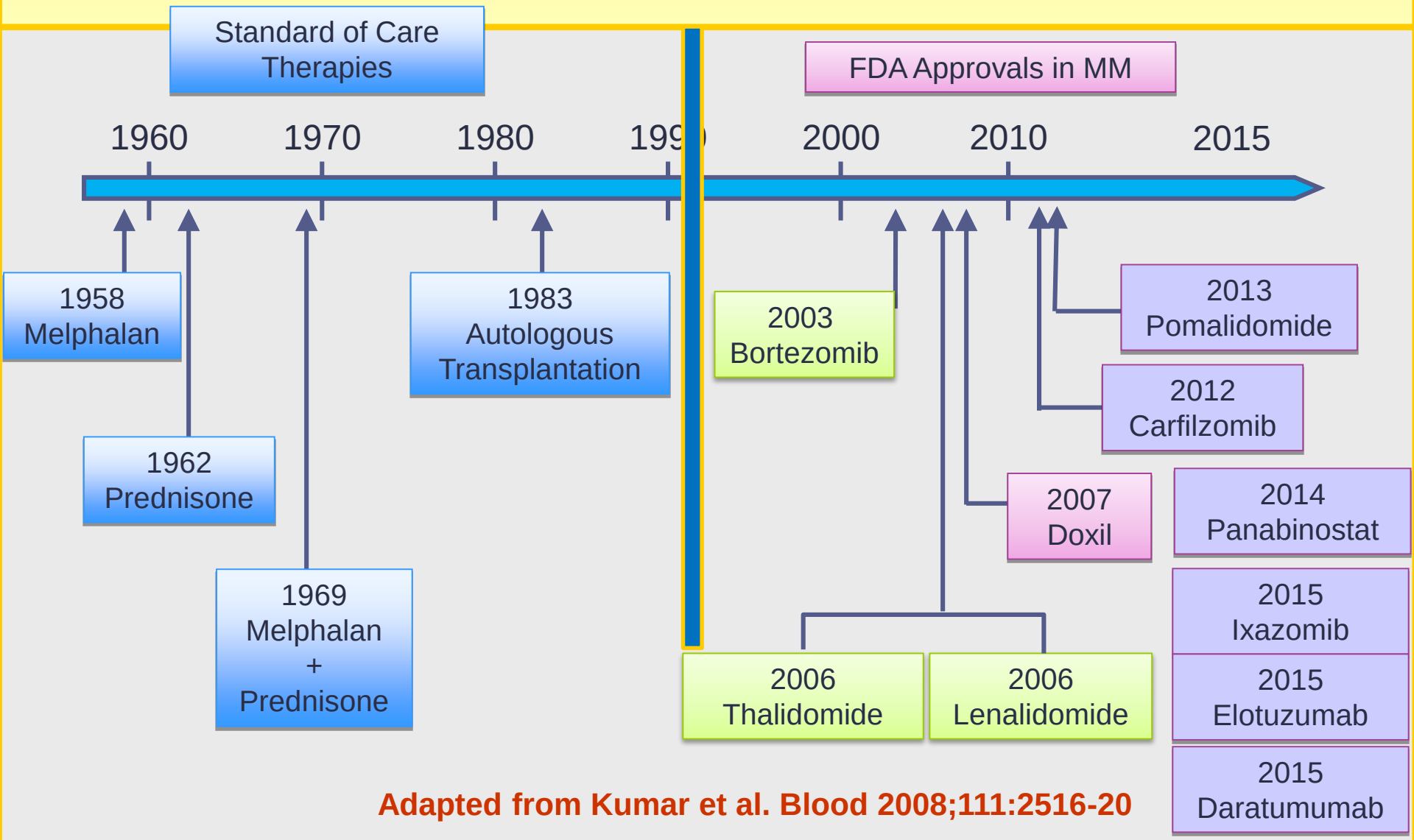


- Autologous Cell Transplantation
  - High-dose melphalan
- CONSEQUENCE: severe immunosuppression in various elements of host defenses
  - Breakdown in skin and mucous membranes: severe mucositis, CVC
  - Severe neutropenia
  - T-cell immunodeficiency after engraftment

Attal et al. N Engl J Med 1996;335:91-7

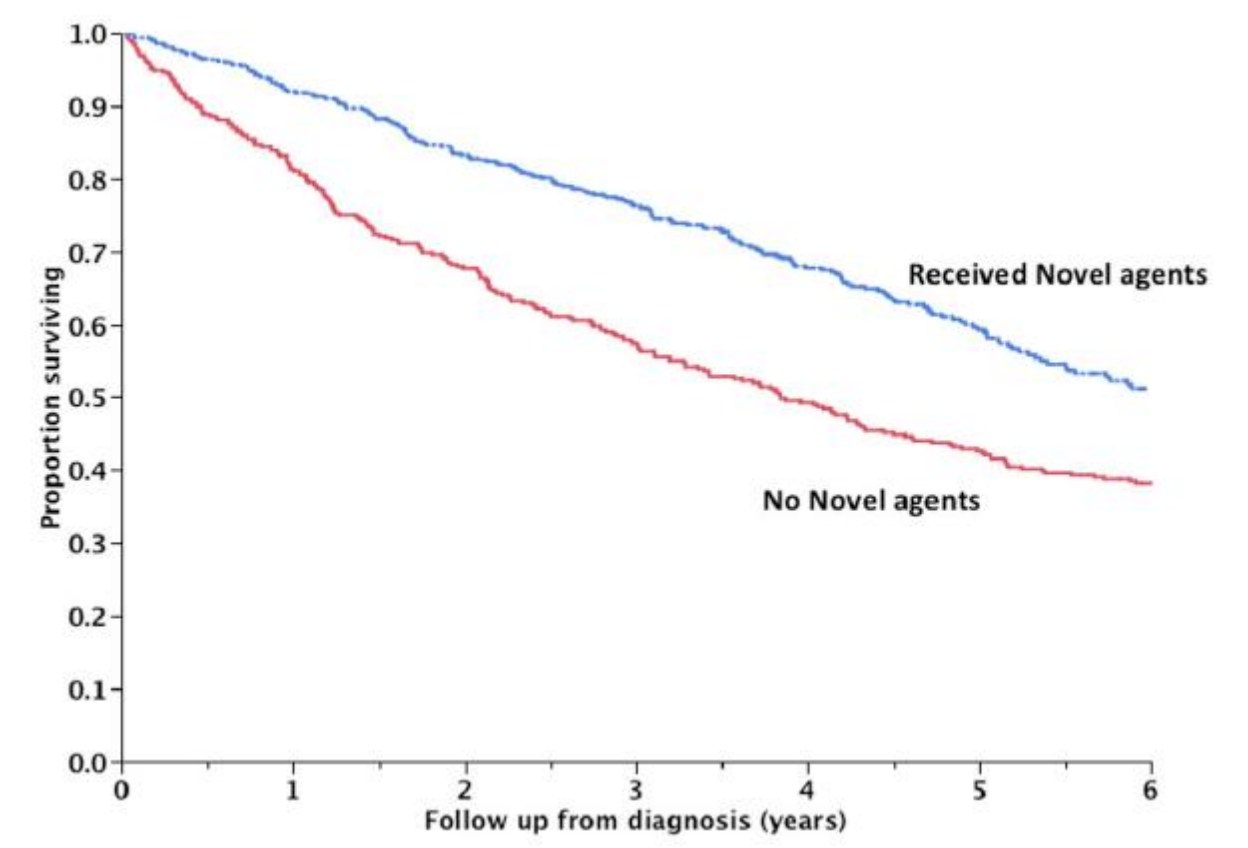
Nucci & Anaissie. Clin Infect Dis 2009;49:1211-25

Therapy for Multiple Myeloma



Adapted from Kumar et al. Blood 2008;111:2516-20

Novel Therapies for Multiple Myeloma and Survival



Kumar et al. Blood 2008;111:2516-20

Multiple Myeloma: Treatment Phases Eligible for HCT

- Induction: 3-4 cycles of combination chemotherapy
- Consolidation: autologous hematopoietic cell tansplantation
- Post-consolidation: 2-4 cycles of combination chemotherapy (+ / -)
- Maintenance: 1-2 drugs given until disease progression or for a fixed period (1-2 years)
- Therapy for relapsed / refractory disease

Multiple Myeloma

Treatment Options

- Conventional chemotherapy
  - Melphalan, cyclophosphamide, bendamustine, vincristine, etoposide, cisplatin, anthracyclines, corticosteroids, others
- Immunomodulators
  - Thalidomide, lenalidomide, pomalidomide
- Proteasome inhibitors
  - Bortezomib, carfilzomib, ixazomib
- Monoclonal antibodies
  - Daratumumab, elotuzumab
- Deacetylase inhibitor
  - Panobinostat

Immunomodulatory Drugs in Multiple Myeloma

	Thalidomide	Lenalidomide	Pomalidomide
Immunomodulation CD4 and CD8	+	++++	+++++
Th1 cytokine production	+	++++	+++++
Suppression of regulatory T-cells	-	+	+
NK and KNT cell activation	+	++++	+++++
Anti-angiogenesis	++++	+++	+++
Anti-inflammatory proprierties	+	++++	+++++
Neutropenia	-	+	+

Infection in Patients Receiving Thalidomide and Lenalidomide

- Thalidomide: no significant differences in the rates of infection compared with other agents
- Lenalidomide: ↑ frequency of neutropenia → ↑ risk of infection
- Lenalidomide: ↑ CD8 T cell responses to viral antigens
  - Vaccine during maintenance phase
    - Lenalidomide
    - Myeloma under control

Teh et al. Blood Reviews 2014;75-85

Proteasome Inhibitors
Bortezomib, Carfilzomib, Ixazomib

- Proteasome: breaks down >80% of intracellular proteins, including those involved in cell cycle, apoptosis, DNA repair and antigen presentation
- Proteasome inhibitors act in cancer cells by
  - Inhibiting proteasomes
  - Activating transcriptor factor NFkB
- Effect of proteasome inhibitors in the normal immunity
  - Depletion of allo-reactive T cells
  - ↓ production of IL-2 and TNF-α
  - ↓ viral antigen presentation

Teh et al. Eur J Cancer 2016;67:21-37

Bortezomib ↑ VZV Reactivation

- Randomized trial, bortezomib vs. dexamethasone in 669 MM patients with refractory disease
  - Herpes zoster: 13% (B) vs. 2% (D)

Richardson et al. N Engl J Med 2005;352:2487-98

- Randomized trial, MP vs. MP + bortezomib in 682 newly diagnosed MM patients
  - Herpes zoster: 13% (MPB) vs. 4% (MP)
    - Incidence reduced to 3% after the introduction of acyclovir prophylaxis

Mateos et al. Blood 2006;108:2165-72

Infection Rates with or without Bortezomib and Lymphocyte Counts

- 139 patients receiving bortezomib-based regimens
- Severe infection in 43 (30.9%)
  - Pneumonia in 70%
  - 10 deaths (7.1%)
- Lymphocytopenia (OR 3.17) associated with severe infection

Jung et al. Int J Haematology 2013;382-7

Multiple Myeloma and Hepatitis B

- 641 MM patients treated with novel agents +/- autologous HCT
  - Hepatitis in 1 of 8 (12.5%) HBV carriers
  - HBV reactivation in 9 of 99 (9.1%) patients with resolved HBV infection
    - Preemptive entecavir → no hepatitis
- MM patients should be screened for HBV at diagnosis and monitored with HBV DNA levels in the serum

Tsukune et al. Ann Hematol 2016;95:1465-72

Bortezomib ↑ Risk of Hepatitis B Reactivation

- Higher risk of Hepatitis B reactivation in MM patients
  - 139 patients receiving bortezomib
    - 27 HBsAg+
      - 22 received lamivudine or entecavir before chemotherapy until 6 months after
      - Reactivation in 6/27 (22%)

Li et al. Leuk Lymphoma 2015;56:1710-7

Daratumumab in Multiple Myeloma

- Anti-CD38 monoclonal antibody
  - CD 38: transmembrane glycoprotein, signal transduction, regulation of cell adhesion
  - Present in myeloid and lymphoid cells; high expression in MM cells
- Anti-myeloma effect
  - Induction of apoptosis
  - Immunomodulatory effect with stromal cells, triggering antibody-dependend cell-mediated cytotoxicity (ADCC) and complement-dependent citotoxicity (CDC)

Sanchez et al. J Hematology & Oncology 2016;9:51-

Elotuzumab in Multiple Myeloma

- Monoclonal antibody againts signaling lymphocytic activation molecule F7 (SLAMF7)
  - Glycoprotein expressed in myeloma and NK cells
- Anti-myeloma effect
  - Activation of NK cells
  - Promotion of antibody-dependend cell-mediated cytotoxicity (ADCC) and complement-dependent citotoxicity (CDC)

Lonial et al. N Engl J Med 2015;373:621-31

Infection in Patients Receiving Daratumumab (D) or Elotuzumab (E) in Multiple Myeloma

- Neutropenia
  - D: 13% vs. 4% control group
  - E: 34% vs. 44% control group
- Lymphocytopenia
  - D: 9.5% vs. 2.5% control group
  - E: 77% vs. 49% control group
- Similar rates of infection comparing MoAb and control groups

➢ No other data on infection

Palumbo et al. N Engl J Med 2016;375:754-66

Lonial et al. N Engl J Med 2015;373:621-31

Panobinostat in Myeloma

- Panobinostat inhibits deacetylation of histones
  - Aberrant recruitment of histone deacetylase by myeloma cells changes gene expression and blocks apoptosis
- Used in combination bortezomib and dexa in relapsed or refractory patients
- Main effect on immunity: neutropenia

Bringhen et al. Clin Lymphoma, Myeloma Leuk 2017 [Epub ahead of print]

Infections with Novel Agents for Myeloma

- Immunomodulators (especially lenalidomide)
  - Immunostimulation, ↑ efficacy of vaccines
  - ↑ frequency of neutropenia
- Proteasome inhobotors
  - ↑ risk for viral infections, VZV, HBV (others?)
- Daratumumab: ↑ neutropenia
- Elotuzumab: ↑ lymphocytopenia
- Panobinostat: ↑ neutropenia

Infection in Multiple Myeloma
What about Cumulative Immunosuppression?

- What impacts the immunity?
  - Multiple courses of chemotherapy including BMT
  - Iron overload associated with multiple transfusions
  - Tons of steroids!!!
  - ↑ co-morbidities, including renal failure, poor performance status, bone disease
  - ↑ age
  - ↑ tumor burden due to refractory disease with ↓↓ immunoglobulins and neutropenia

Nucci & Anaissie. Clin Infect Dis 2009;49:1211-25

Infection in Multiple Myeloma
What about Cumulative Immunosuppression?

- What are the consquences?
  - Infections caused by “unusual” pathogens
    - Invasive fungal disease (aspergillosis, fusariosis, mucormycosis)
    - Symptomatic CMV reactivation
    - *Pneumocystis jirovecii* pneumonia
    - Severe viral respiratory tract infections
    - Frequent VZV reactivation

Nucci & Anaissie. Clin Infect Dis 2009;49:1211-25
Teh et al. Support Care Cancer 2015;23:1901-6

Pattern of Infection in Multiple Myeloma Related to Cumulative Immunosup-pression

- Cohort of 199 MM patients at a single center, treated with various regimens in different phases
- Prophylactic measures
  - Acyclovir or valacyclovir if bortezomib or HCT (3 mo)
  - Fluconazole if HCT (until engraftment)
  - SMZ/TMP if steroids (>20 prednisone for >4 weeks)

Teh et al. Br J Haematol 2015;171:100-8

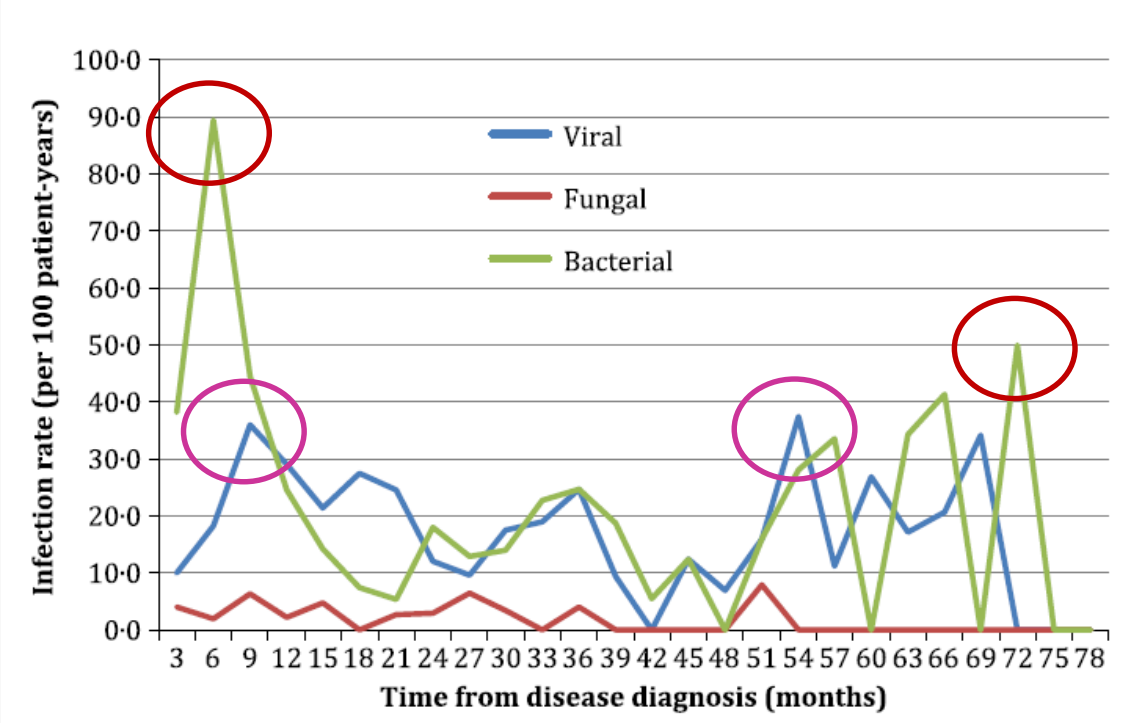
Pattern of Infection in Multiple Myeloma Related to Cumulative Immunosup-pression

- 771 episodes of infection (1.33 episode per 100 patients.year)
  - 281 (36.4%) microbiologically defined
    - 54% bacterial (47% GN, 39% GP, 14% multiple)
      - *Str pneumoniae* only 5.3%!!!
    - 40% viral (47% respiratory, 36% VZV, 12% HSV, 4% CMV)
    - 6% fungal (n=16: Pneumocystis (6), Aspergillus (2), Fusarium (1))

Teh et al. Br J Haematol 2015;171:100-8

Pattern of Infection in Multiple Myeloma Related to Cumulative Immunosup-pression

- Bacterial infection: 2 peaks of incidence
  - 4-6 months
  - 70-72 months
- Viral infection: 2 peaks of incidence
  - 7-9 months
  - 52-54 months
- All infections resulting in death occurred during disease progression!!!



Teh et al. Br J Haematol 2015;171:100-8

Pattern of Infection in Multiple Myeloma Related to Cumulative Immunosup-pression

- Second peak of incidence related to disease progression

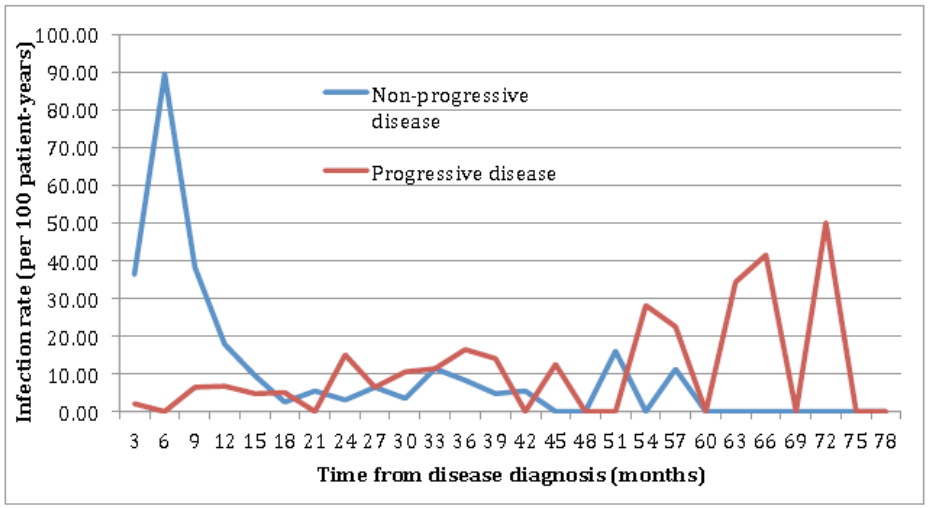


Figure 1a: Bacterial infection

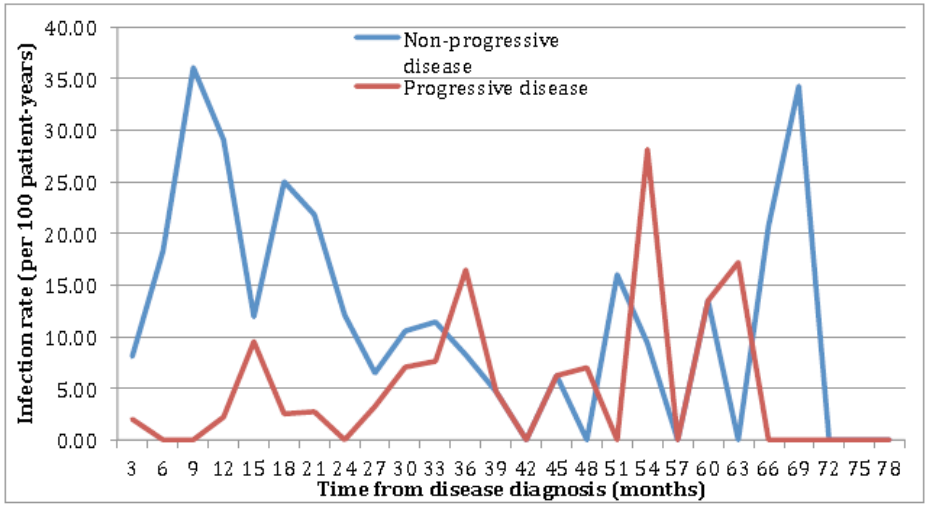


Figure 1b: Viral infection

Teh et al. Br J Haematol 2015;171:100-8

Risk Factors for Infection in Multiple Myeloma in Different Phases of the Treatment

Induction phase	HR (95% CI)
Disease stage (ISS)	1.59 (1.13 – 2.24)
Cumulative steroids (pred) dose (1 m)	
0 – 800 mg (~25 mg/d)	5.36 (2.32 – 12.39)
>800 – 1600 mg (~25-50 mg/d)	7.67 (2.36 – 24.96)
>1600 mg (>50 mg/d)	9.38 (1.39 – 63.27)

A full dexamethasone course of 40 mg/d x 4d x 3/month = 3000 mg pred/m

Teh et al. Br J Haematol 2015;171:100-8

Risk Factors for Infection in Multiple Myeloma in Different Phases of the Treatment

Disease progression	HR (95% CI)
Number of lines of therapy	2.46 (1.39 – 4.33)
Intensive combination chemotherapy	4.05 (1.25 – 13.11)
IV cyclophosphamide	5.43 (1.63 – 18.01)
Cumulative steroids (pred) dose (1 m)	
1 – 1600 mg (~50 mg/d)	2.62 (1.24 – 5.53)
>1600 – 3200 mg (~50-100 mg/d)	11.60 (4.33 – 31.06)
>3200 mg (>100 mg/d)	5.66 (1.00 – 32.30)

A full dexamethasone course of 40 mg/d x 4d x 3/month = 3000 mg pred/m

Teh et al. Br J Haematol 2015;171:100-8

What should I Ask Before Seeing a Myeloma Patient?

1. When was myeloma diagnosed?
2. What previous therapies did the patient receive?
3. What infections has the patient developed so far?
4. What and when was the more recent treatmant?
5. What is the current status of disease?
6. How much steroids has the patient received lately?
7. What are the absolute neutrophil and lymphocyte counts?
8. What co-morbidities are present?

So, What Can We Do to Prevent Infection?

Prophylactic agents

1. Antibacterial
   - Quinolone during neutropenia after autologous HCT
   - Any prophylaxis late phases with advanced disease?
2. VZV
   - If bortezomib: acyclovir – 200-400 mg PO 1-2x/d or valacyclovir 500 mg PO 1-2x/d
   - Other proteasome inhibitors, no data, but prophylaxis recommended

So, What Can We Do to Prevent Infection?

Prophylactic agents

3. Herpes simplex
   - During pre-engraftment period of autologous HCT: acyclovir 250 mg/m^2 3x/d

4. *Pneumocystis jirovecii*
   - If steroids for >4 weeks
   - SMZ/TMP 160/800 daily or 3x/week

5. Antifungal prophylaxis
   - During autologous HCT, optional, fluconazole 400 mg/d
   - Extended spectrum azoles ???

So, What Can We Do to Prevent Infection?

Vaccines

Response to vaccine may be better in lenalidomide recipients

- Vaccinate as early as possible
- Live vaccines contraindicated and should be avoided in close contacts
  - Yes in pts receiving lenalidomide maintenance?

Pandit et al. ID week 2016 (#2327)

1. Pneumococcal
   - PCV13 followed by PPSV23 ≥8 weeks after
     - If previous PPSV23, wait at least 1 year to give PCV13
2. Haemophylus influenza B
3. Seasonal Influenza (yearly)
   - Patients and household members (healthcare workers and caregivers)

Infection in Multiple Myeloma

- Biphasic pattern of infection
  - 1st few months from diagnosis, bacterial infections
  - Refractory disease, bacterial, viral and fungal infections
- Multiple defects in the immune system, cumulative immunosuppression
- Novel agents
  - Immunomodulators: infection associated with neutropenia, enhanced response to vaccine
  - Proteasome inhibitors: viral infections
  - Monoclonal antibodies: little information