Treatment Breakthroughs in Multiple Myeloma

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Timeline

- 1844: First documented case of myeloma (Solly et al. Med Chir Trans London)
- 1845: BJP was described
- 1895: Morphologic description of plasma cells
- 1928: First large series of myeloma patients
- 1939: Serum protein spike identified
- 1947: Urethane used for the Rx of myeloma (Alwall et al. Lancet)
- 1956: Kappa and lambda light chains identified
- 1975: Durie-Salmon staging system
- 2005: International Staging System
- 2000+: Cytogenetic and molecular classification
- 2011: Genome sequencing of myeloma cell (Chapman et al. Nature)

Treatment Timeline

- 1958: First report of successful use of Melphalan (Blokhin et al. Ann NY Acad Scie)
- 1962: First report of successful use of Corticosteroids (Maas RE Cancer Chemother Rep)
- 1969: Melphalan + Prednisone established as standard induction in a randomized trial (Alexanian R et al. JAMA 1969)
- 1982: First successful syngeneic transplantation for myeloma (Osserman EF, R Storb R. Acta Haematol)
- 1983: First high-dose melphalan (T McElwain, R Powles)
- 1999: First report of successful use of Thalidomide (Singhal S, Barlogie B et al.)
- 2002:First report of successful use of Bortezomib (Orlowski RZ et al.)
- 2002: First report of successful use of Lenalidomide (Richardson PG, Anderson KC)
- 2009: First report of successful use of Carfilzomib (O'Connor , Orlowski R. Clin Cancer Res)
- 2009: First report of successful use of Pomalidomide (Lacy M, Rajkumar SV. JCO)

blood
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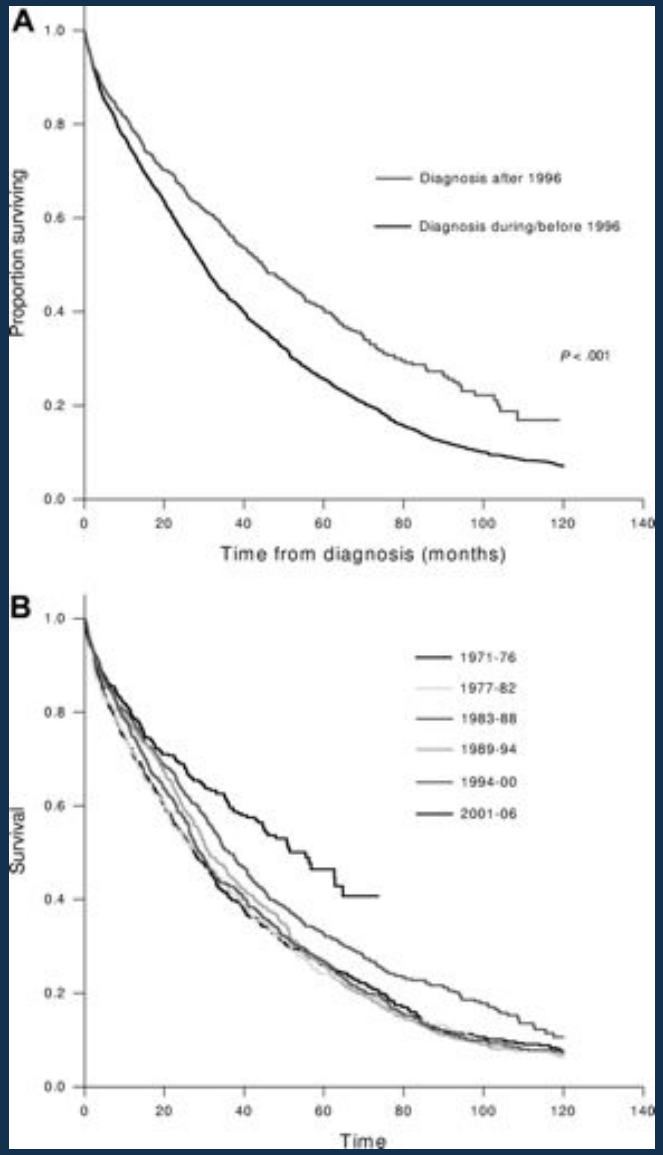
Overall survival from diagnosis of multiple myelomas.



Kumar S K et al. Blood 2008;111:2516-2520

Improvement in Myeloma Outcome

- The unequivocal evidence that the outcome of myeloma has significantly improved within the last decade is mainly due to:
  - Optimal use of auto-HCT
  - Use of novel agents: thalidomide, lenalidomide and bortezomib
  - Improvements in supportive care
  - *Better understanding of disease biology and emergence of targeted therapies

Thalidomide

- Thalidomide was marketed as a sedative in the 1950s
- In 1961, it was discovered to be teratogenic, affecting 10,000 infants and was taken off the market
- In 1997, Dr. Barlogie started a trial due to its antiangiogenic properties in myeloma
- In 84 patients treated, response rate was 32% (Singhal S et al. NEJM 1999)

Lenalidomide

- An analog of thalidomide developed to enhance efficacy and to minimize toxicity
- Overall response rate (MR) with single agent lenalidomide was 71% in patients with relapsed or refractory myeloma (Richardson PG et al. Blood 2002)
- In an upfront trial at Mayo Clinic, lenalidomide + dexamethasone was associated with response in 31/34 (91%) newly diagnosed patients (Rajkumar SV et al. Blood 2005)
- It was approved by the FDA for myeloma in 2006

Bortezomib

- Inhibition of proteasome causes apoptosis, predominantly in the malignant and proliferating cells
- Robert Orlowski led the initial clinical trial in hematologic malignancies, where it showed striking anti-myeloma (9/9 patients) activity (Orlowski RZ et al. JCO 2002)
- It was approved by the FDA for myeloma in 2003

Putting it all together

- Advances in Induction Therapy
- Advances in Stem Cell Transplantation
- Advances in Post-transplant Consolidation and Maintenance
- Advances in Supportive Care
- Advances in Relapsed Disease

Induction Therapy for Transplant Eligible Patients: NCCN Category 1

- Bortezomib + Dexamethasone (Harrousseau J et al. JCO 2010)
  - BD vs. VAD (482 pts.)
  - CR/nCR: 14.8 vs. 6.5%
  - PFS: 36 vs. 29.7 months
  - Improved EFS and OS in patients with t(4;14). Avet-Loiseau H. JCO 2010
- Bortezomib + Doxorubicin + Dexamethasone (Sonneveld P et al. HOVON. ASH 2010*)
  - PAD vs. VAD
  - Superior ORR and PFS with PAD

Induction Therapy for Transplant Eligible Patients: NCCN Category 1

- Bortezomib + Thalidomide + Dexamethasone (*Rosinol L. PETHEMA. ASH 2010)
  - GIMEMA Trial . Cavo M et al. Lancet 2010;
  - VTD vs. TD (480 patients)
  - CR/nCR (31% vs. 11%)
- Lenalidomide + Dexamethasone. ()
  - SWOG Trial. Zonder J et al. SWOG. ASH 2007*;
    - LD vs. D
    - CR: 22.1% vs. 3.5% (study terminated)
  - ECOG. Rajkumar SV. ECOG. Lancet Oncology 2010
    - LD vs. Ld
    - ORR: 79% vs. 66%
    - 1-year OS: 87% vs. 96% (*trial stopped)

Induction Therapy for Transplant Ineligible Patients: NCCN Category 1

- Lenalidomide + Low-Dose Dexamethasone
  - (Zonder J et al. SWOG. ASH 2007*; Rajkumar SV. ECOG. Lancet Oncology 2010)
- Melphalan + Prednisone + Thalidomide
  - (Palumbo A et al. Lancet 2006; Facon T et al. Lancet 2007; Wijermans P et al. JCO 2010)
- Melphalan + Prednisone + Bortezomib
  - (San Miguel J et al. VISTA trial. NEJM 2008)
- Melphalan + Prednisone + Lenalidomide
  - (Palumbo A. NEJM 2012)

HDT With ASCT vs Conventional Chemotherapy

- 4 published trials compared conventional chemotherapy (CC) with HDT in newly diagnosed Durie-Salmon stage II/III MM

Study	Age (yr)	Tx	n	CR (%)	Median EFS (mo)	Median OS (mo)
Attal et al[1] (IFM90)	<65	CC	100	5*	18*	44*
		HDT	100	22*	28*	57*
Fermand et al[2] (MAG91)	55–65	CC	91	-	19*	50
		HDT	94	-	24*	55
Bladé et al[3] (PETHEMA)	<65	CC	83	11*	33	64
		HDT	81	30*	42	72
Child et al[4] (MRC7)	<65	CC	200	8*	20*	42*
		HDT	201	44*	32*	54*

*Significant *P* value

1. Attal M et al. *N Engl J Med*. 1996;335:91
2. Fermand J et al. *Blood*. 1998;92:3131
3. Bladé J *et al*. *H* *Blood 2005*
4. Child JA et al. *N Engl J Med*. 2003;348:1875

Auto HCT Improves CR Rates When Used with Newer Agents

- Harousseau J et al. JCO 2010
  - 482 patients enrolled: Median F/U 32 months
  - Bortezomib + Dex ± DCEP vs. VAD ± DCEP
  - Post induction CR: 14.8 vs. 6.4%
  - Post auto HCT (1 or 2) CR: 35 vs. 18%
  - Median PFS: 36 vs. 29.7 months (p=0.06)
- Cavo M et al. Lancet 2010
  - 480 patients enrolled
  - Induction: VTD vs. TD x 3
  - Post induction CR: 31% vs. 11%
  - Tandem auto
  - Consolidation: VTD vs. TD x 2

Maintenance Therapy: NCCN Category 1

- Thalidomide
  - (Attal M et al. Blood 2006; Spencer A et al. JCO 2009)
- Lenalidomide
  - (Attal M et al. NEJM 2012; McCarthy P et al. NEJM 2012)

Thalidomide Maintenance

- Thalidomide
  - Attal et al. *Blood 2006* (597 patients)
    - Observation vs. Pamidronate vs. Thalidomide
    - 3-year EFS: 38, 39 and 51%
    - 4-year OS: 77, 74 and 87%
  - Spencer et al. *JCO 2009* (269 patients)
    - Prednisolone vs. Thalidomide + Prednisolone
    - 3-year PFS: 23 vs. 42%
    - 3-year OS: 75 vs. 86%
  - 1 trial (MRC IX) showed improvement in PFS but not OS
    - Morgan GI et al. *Blood 2012*

Maintenance: Lenalidomide vs. Placebo

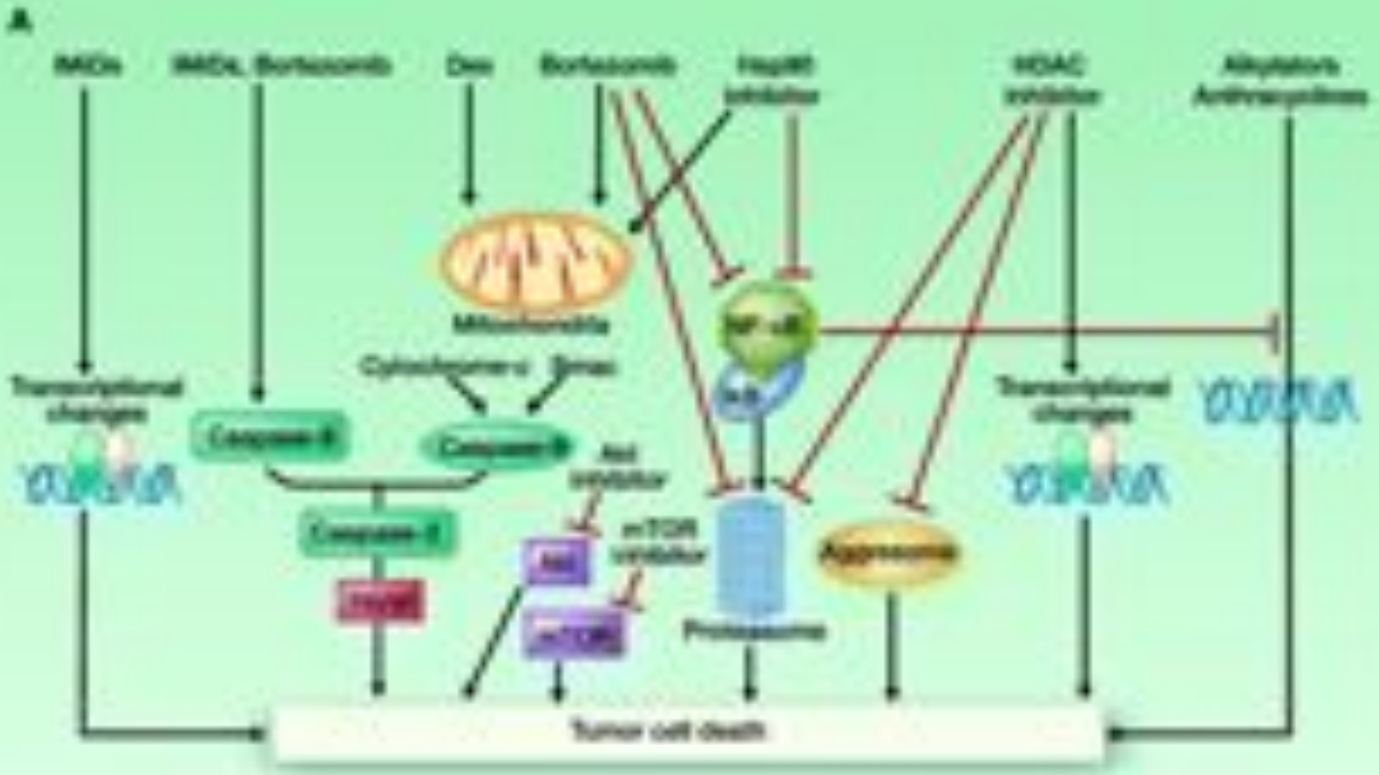
- Attal et al. IFM Trial. NEJM 2012
  - 614 patients
  - Median EFS: 40 vs. 23 months
- McCarthy et al. CALGB trial. NEJM 2012
  - 568 patients
  - Median TTP: 46 vs. 27 months
  - OS: p=0.03
- Lenalidomide is associated with:
  - neutropenia
  - *Increased second primary malignancies

Supportive Care

- Bisphosphonates
  - Reduces SREs
    - Morgan G. MRC Myeloma IX. Lancet Oncol.2011
  - Associated with improved survival in the MRC trial
    - Morgan G. MRC Myeloma IX. Blood.2012
- Vertebroplasty/Kyphoplasty
  - Pain control in vertebral compression and collapse
- Anti-microbials

Emerging Anti-Myeloma Therapies

- New Proteasome Inhibitors
  - Carfilzomib
    - Approved by the FDA in August 2012
  - MLN9708
    - Oral proteasome inhibitor
    - Promising single agent activity
- New IMiDs
  - Pomalidomide
    - Most potent IMiD
    - Active against revlimid and bortezomib-refractory patients
    - Myelosuppression is the main toxicity



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Rationally Based Combination Therapies

- Bortezomib and Hsp 90 inhibitors
- Bortezomib and Doxil
- Bortezomib and NPI-0052 (proteasome inh)
- Bortezomib and perifosine (Akt inh)
- Bortezomib and Bcl-2 inhibitor
- Bortezomib and p38 MAPK inhibitor
- Bortezomib and HuLuc63 (anti-CS-1 ab)
- Bortezomib and LBH 589 (HDAC inh)
- Bortezomib and SAHA (HDAC inh)
- Bortezomib and CCI-779 (mTOR inh)
- Lenalidomide and mTOR inhibitors
- Lenalidomide and Anti-CD40 antibody
- Lenalidomide and Doxil
- Lenalidomide and HuLuc63 (anti-CS-1 ab)
- Lenalidomide and LBH 589 (HDAC inh)
- Lenalidomide and perifosine (Akt inh)
- Lenalidomide and Bevacizumab
- Lenalidomide and Vaccines
- Lenalidomide and carfilzomib
- Lenalidomide and NPI-0052
- Lenalidomide and SAHA (HDAC inh)

Lenalidomide and Bortezomib +/- Dex

Targeted Therapies

- HDAC Inhibitors: synergistic with proteasome inhibitors
  - Vorinostat
    - (Richardson PG et al. Leuk Lymphoma 2008)
  - Panobinostat
- mTOR Inhibitors
  - Everolimus:
    - Mahindra A et al. ASH 2010
  - Temsirolimus:
    - Ghobrial I et al. Lancet Oncol. 2011
- PI3 Kinase Pathway Inhibitor
  - Perifosine:
    - Richardson PG et al. JCO 2011

Immunotherapies

- Antibodies
  - Elotuzumab (Anti- CS1)
  - Siltuximab (Anti-IL6)
  - Anti-CD38 antibody
  - Anti KIR antibody (to neutralize their inhibitory effect on NK cells)
- Vaccines
  - Idiotype
  - Dendritic cell
- Cellular Therapy
  - Vaccine-primed , ex-vivo activated T lymphocytes
    - hTert/survivin: Rapoport A et al. Blood 2011

Future Directions

- Development of Personalized, risk-adapted therapy based on specific molecular or genetic pathways involved in an individual patient