MANAGEMENT OF ANEMIA AND NEUROLOGICAL COMPLICATIONS IN MULTIPLE MYELOMA

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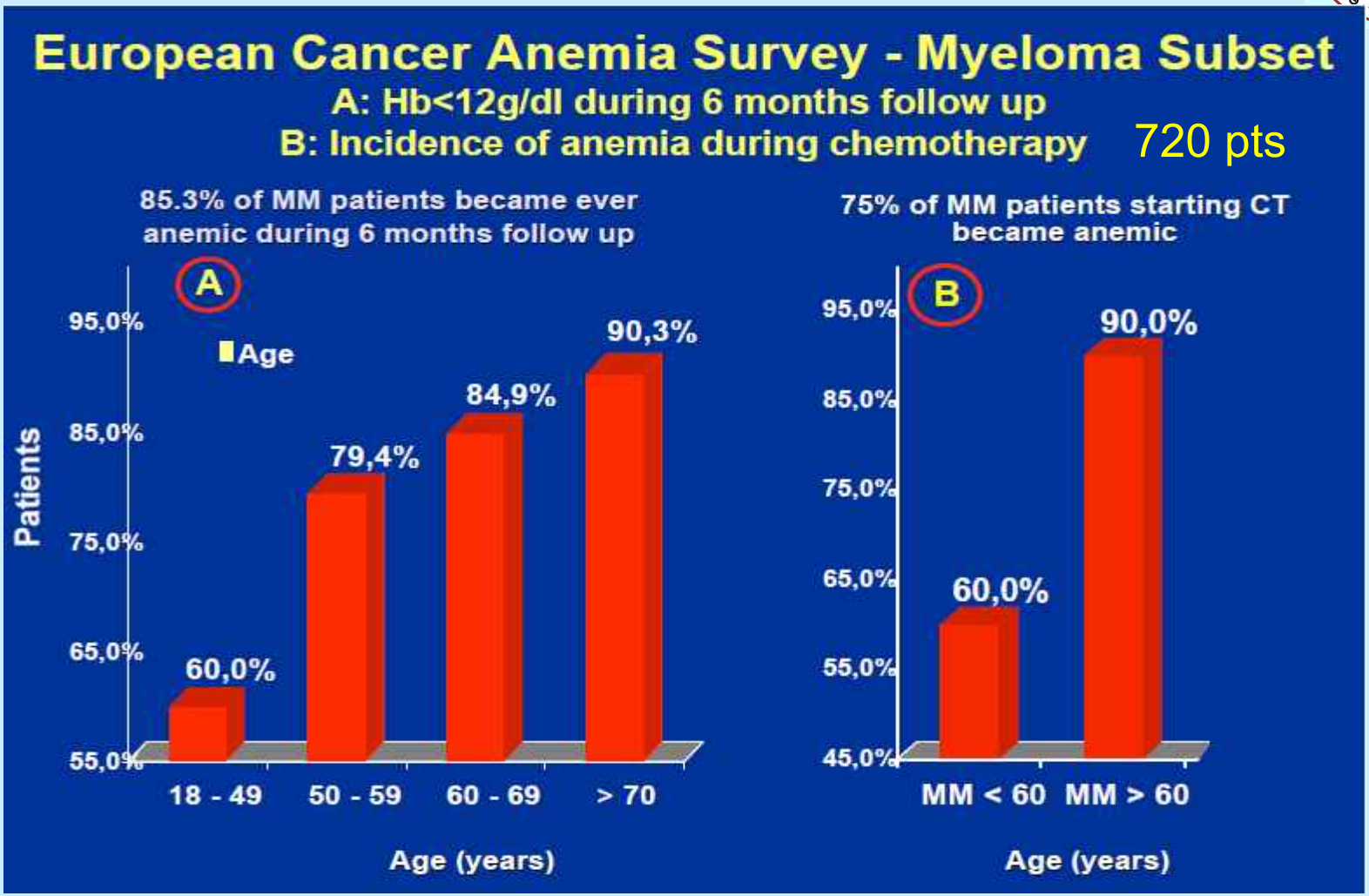
Prevalence of anemia in MM

Study	# of Pts	Hb	Prevalence
Kyle, 1975	869	<12 g/dL	73%
Ludwig, 1994	292	<12 g/dL	72%
San Miguel, 1995	120	<10.5g/dL	68%
Zervas, 2009 (unpublished data)	503	<12 g/dL	77%



Grade 3+4: 22%, 6.4%, 41% (CT, RT, CT/RT)

Ludwig H, et al. Eur J Cancer, 2004; 40: 2293-2306
Birgergard G, et al Eur J Haematol 2006; 77: 378-386

Treatment-related anemia in the era of novel agents and combinations

Study	Regimen	Anemia grade 3+4 (%)
Facon, Lancet, 2007	MP vs MPT	14 vs14
Palumbo, Lancet, 2006	MP vs MPT	4 vs 3
Richardson (SUMMIT) bjh, 2003	Vel ± Dexa	8
Richardson (APEX), Nejm, 2005	Vel vs Dexa	10 vs 11
San Miguel, (VISTA), Nejm, 2008	MP vs MPV	28 vs 19
Palumbo, Blood, 2007	VMPT	16
Rajkumar, Blood, 2005	RD	6
Dimopoulos (Weber), Nejm, 2007	RD vs Dexa	9 (13)
Knop, Blood, 2009	RAD	16.5
Kyriakou, Davies, Morgan, bjh, 2005, 2007, 2007	CDT, CDV, CDR	Not reported

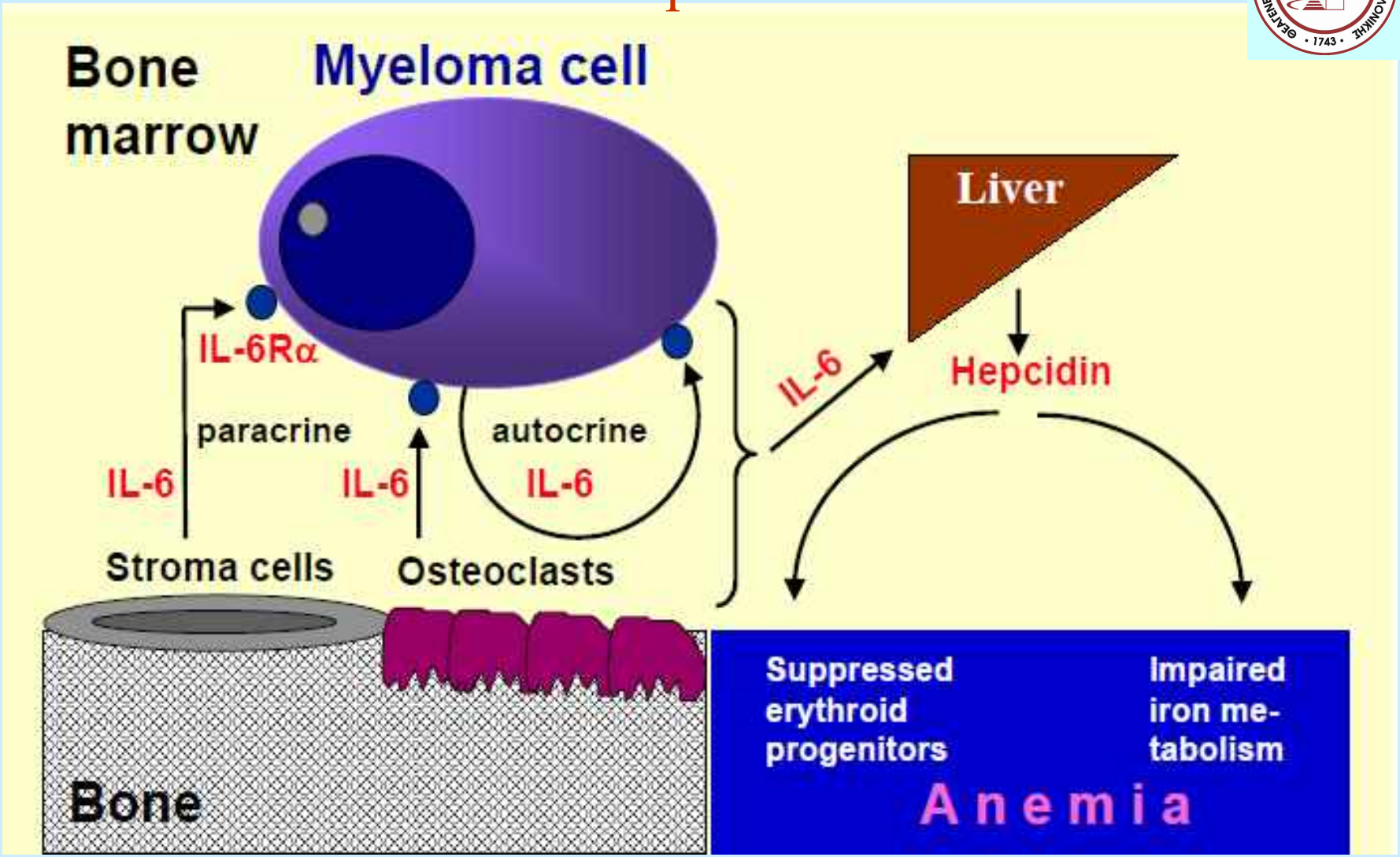
Pathogenesis of anemia in MM

- ❑ Bone marrow infiltration
- ❑ Renal insufficiency
- ❑ Chemo/radiotherapy
- ❑ Hemolysis
- ❑ Hypervolemia, infection, nutritional deficiencies
- ❑ Wnt-inhibitors-induced suppression of hematopoiesis

- ❑ Anemia of Chronic disease
- ✓ Inadequate levels and blunted response to endogenous EPO
- ✓ ↑ Pro-inflammatory cytokines (IL-1, TNFa, IFN-γ, IL-6)
- ✓ ↓ Number of erythroid precursors
- ✓ FAS-L/TRAIL induced apoptosis
- ✓ Dysregulation of iron metabolism induced by the iron regulator, hepcidin

Mittleman M. Clin Lymphoma, 2003; 4: 23-29
Weiss G & Goodnough L. N En J Med, 2005; 352: 1011-1023
Stewart JP & Shaughnessy JD. J Cell Biochem, 2006; 98: 1-13
Silvestris F, et al. Blood, 2002; 99: 1305-1313

Association of hepcidin with MM



Nemeth E, et al. Blood, 2003; 101: 2461-2463
Nemeth E, et al. J Clin Invest, 2004; 113: 1271-1276
Dallalio G, et al. Blood 2005; 107: 2702-2704

➢Hepcidin mRNA is up-regulated by both IL-6 dependent and independent mechanisms in MM and it may play an etiological role in the development of anemia

▪Baseline serum hepcidin is negatively correlated with anemia and significant disease indicators in MM (ISS, β2M)

▪Anti-myeloma treatment and more profoundly, IMiDs-combinations significantly reduced hepcidin

✓Baseline serum hepcidin is an independent predictor for response to ESAs in anemic cancer patients (including MM)

➢*Sharma S, Nemeth E, Chen YH, et al. Clin cancer Res, 2008; 14: 3262-3267*
▪*Katodritou E, Ganz T, Terpos E, et al. Am J Hematol, 2009; 84: 524-526*
✓*Ukarma L, Johannes H, Beyer U et al. Clin Chem, 2009; 55: 1354-1360*

Management of anemia in MM

- Disease control
- Erythropoiesis-stimulating agents (ESAs)
- IV iron supplementation (monotherapy?)
- RBC-transfusions

Prospective Randomized studies with ESAs in Myeloma (MM) and Lymphomas (L)

Author (year)	Response criteria	# of pts	ESAs	Duration of ESAs (wks)	Response %
Cazzola (1995)	Hb≥2g/dl	146(MM/L)	Epoetin β	8	62
Garton (1995)	Hct=38%	25 (MM)	Epoetin a	24	45
Dammaco (2001)	Hb≥2g/dl	145 (MM)	Epoetin a	12	58
Osterborg (1996)	Hb≥2g/dl No transfusion	65(MM)	Epoetin β	24	60
Osterborg (2002)	Hb≥2g/dl No transfusion	349(MM/L)	Epoetin β	16	67
Hedenus (2003)	Hb≥2g/dl No transfusion	344 (MM/L)	Darbepoetin a	12	60
Cazzola (2003)	Hb≥2g/dl No transfusion	241 (MM/L)	Epoetin β	16	72

- Response to ESAs is independent from disease response

Demetri GD, et al. J Clin Oncol, 1998;16:3412-3425

- 50-60% reduction in transfusion need

Dammaco F, et al. Br J Haematol, 2001; 113: 172-179
Osterborg A, et al. J Clin Oncol, 2002; 20: 2486-2494
Hedenus M, et al. Br J haematol 2003; 122: 394-403

- Improvement of QoL? is controversial

Osterborg A, et al. J Clin Oncol, 2002; 20: 2486-2494
Straus DJ, et al. Cancer, 2006; 107: 1909-1917

- ESAs unresponsiveness: ≈30% (Functional Iron deficiency)

Goodnough L. Exp Hematol, 2007; 35: 167-172

- Predictors for response? Necessary. None established

Littlewood T, et al. Oncologist, 2003; 8: 99-107
Katodritou E, et al. Br J Haematol, 2008; 142: 3-10

Prognostic models for response to ESAs

Author	Ludwig (1994)	Henry (1995)	Cazzola (1995)	Cazzola (1996)	Katodritou (2007)
# of pts	76	132	48	48	41
Neoplasm	Solid/MM/ Lymphomas	Solid	MM/ Lymphomas	Solid/MM/ Lymphomas	MM/ Lymphomas
Response (%)	50	55	65	58	66
Prognostic model	EPO<100mU/ml Hb≥0.5g/dl (wk2)	retics≥ 40000/μL Hb≥0.5g/dl (wk2)	Hb≥0.3g/dl (wk2) b. EPO O/P < 0.9	sTfR>25% (wk2) b.EPO <50mU/ml	Hypochromic erythrocytes <5% alone or in combination with retics wk2> 50,000/μL
Sensitivity (%)	42	19	97	88	81
Specificity (%)	100	88	76	95	93
PPV(%)	100	67	88	96	95
NPV(%)	62	47	93	88	72

ESAs and IV iron supplementation

Study	# of pts	Diagnosis	Iron status	Randomisation	Response
Aurbach (2004)	157	solid	Ferr<450ng/mL	Yes (ESAs vs ESAs +oral iron vs ESAs + IV iron)	68% vs 36 vs 25
Katodritou (2007)	41	MM/L	Stainable iron	No (ESAs+ IV iron non-responders)	83% after IV iron
Hedenus (2007)	67	LPDs	Stainable iron	Yes ESAs vs ESAs+ IV iron	93% vs 53%
Henry (2007)	187	Solid	Ferr>100ng/mL TSAT>15%	Yes (ESAs vs ESAs+ oral vs ESAs+ IV iron)	73% vs 45% vs 41
Bastit (2008)	396	Solid	Ferr>10ng/mL TSAT>15%	Yes ESAs ± oral iron vs ESAs+ IV iron	86% vs 73%
Pedrazzoli (2008)	149	Solid	Ferr>100ng/mL TSAT>20%	Yes ESAs vs ESAs+ IV iron	77 vs 62

IRE indices at baseline	Sensitivity %	Specificity%	PPV%	NPV%	Accuracy%
HYPO% (≥5%)	50*	100	100	79	83
TSAT% (<20%)	55	28	60	25	46
sFerritin (<100ng/ml)	36	85	56	72	68

* HYPO% sensitivity increases over time up to 90%

Katodritou E, et al. Ann Hematol, 2007; 86: 369-376
Katodritou E, et al. Hematologica 92: (S 1): 28, 2007

Iron supplementation improves anemia response to ESAs, however, more firm Iron-restricted erythropoiesis (IRE) criteria are needed in order to avoid its possible adverse effects

Katodritou E, et al. Am J Hematol, 2008; 83: 512-523

IV iron monotherapy in MM

Anemic MM patients with IRE planned to receive anti-myeloma therapy

Treatment for MM

↓

1) Tumor reduction (↓IL6 and other cytokines)

2) Improvement of erythropoietic activity

↓

Hepcidin reduction

Facilitating iron delivery and utilization →

IV iron (concomitant with anti-myeloma treatment)

↓

RBC hemoglobinization

(iron not trapped in the macrophages)

↓

Anemia recovery

Katodritou E, et al. Greek Myeloma Study Group, 2009

What about safety of ESAs use in cancer?

ESAs and risk for VTEs

YES:

✓Meta-analysis in 9,353 cancer patients RR: 1.67

Bohlius J, et al. J Natl Cancer Inst, 2006; 98: 708-714

✓Meta-analysis in 8,172 cancer patients RR: 1.57

Bennet AM, et al. JAMA, 2008; 299: 914-924

✓Pooled analysis from all randomized studies of darbepoetin including 2,122 cancer patients with chemotherapy-induced anemia HR: 1.57

Ludwig et al, J Clin Oncol, 2009; 27: 2838-2847

NO

✓Meta-analysis in 2,301 cancer patients: non-statistical trend for VTEs (higher risk in patients with higher Hb levels)

Aapro M, et al. Br H Cancer, 2008; 99: 14-22

Adverse outcomes associated with ESAs

Study	Diagnosis (Treatment)	# of pts enrolled (target #)	ESAs	Adverse Outcome
Henke 2003	Head & neck (RT)	351	Epoetin beta	HR for progression:1.69 (p=0.007); for death: 1.39 (p=0.02)
Leyland-Jones 2005	Breast (on-therapy)	939	Epoetin alfa	1y survival vs placebo: 70% vs 76% (p=0.01)
Wright 2007	Lung (off-therapy)	70 (300)	Epoetin alfa	OS vs placebo: 63 vs 129d HR for death: 1.84 (p=0.04)
Goldberg 2007	Head & neck (RT)	522 (600)	Darbepoetin	10% increase in progression (p=0.01); trend towards decreased survival (p=0.08)
Smith 2008	Solid &Non-myeloid hematological (off-therapy)	989	Darbepoetin	Shorter OS. HR for death: 1.30 (p=0.008) HR for death for 119 pts MM/L> 2
Lymphoid Cancers anemia study	LPDs (on-therapy)	344	Darbepoetin	Shorter OS. HR for death:1.37 (p=0.04)

FDA in the USA: ESAs after 2008 safety review

- On July 31, the FDA orders safety-related changes for anaemia drugs
- ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure
- ESAs should not be initiated if the patient's haemoglobin is above 10 g/dL

ASH/ASCO recommendations for ESAs use in cancer

- ESAs could be used only if Hb≤10g/dL
- Target hemoglobin should not exceed 12g/dL
- In non-myeloid hematological malignancies ESAs are recommended only in case that anemia does not improve over treatment
- Transfusion is still an acceptable therapeutic option
- The risk for VTEs should be carefully weighted especially in MM patients who often receive IMiDs and dexamethasone or anthracyclines

Rizzo JD, et al. J Clin Oncol, 2008; 26: 132-149

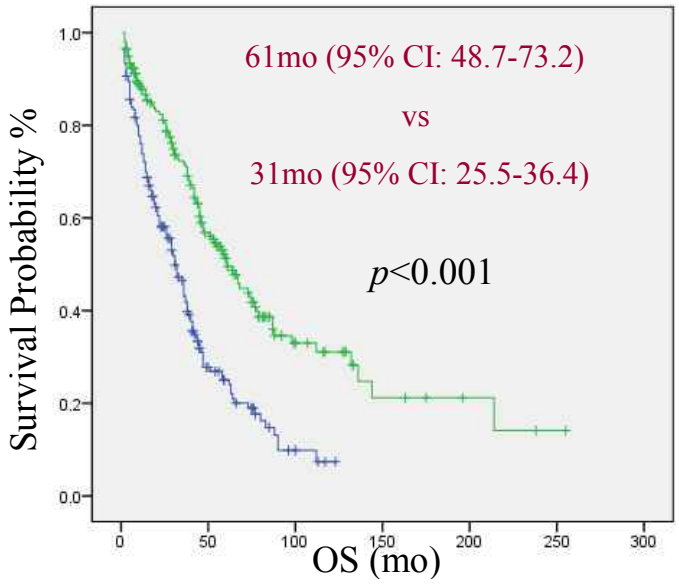
Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomized trials

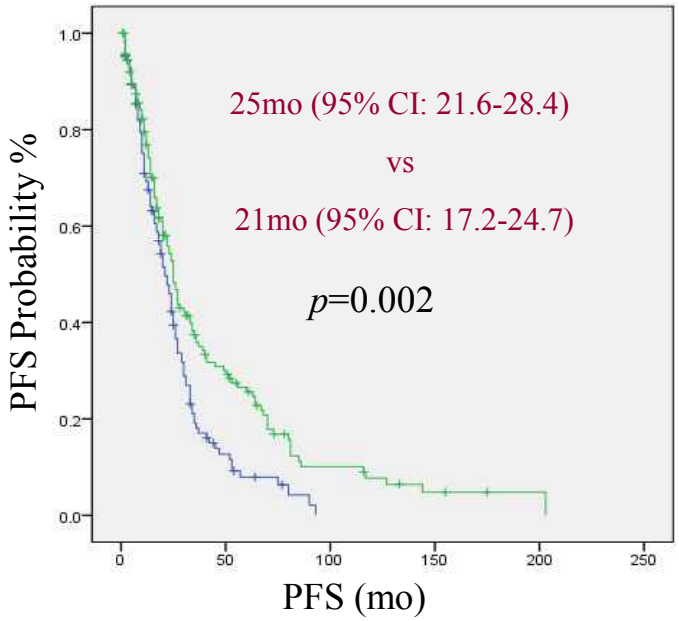
- ESAs treatment in cancer patients increased on-study mortality by 17% and worsened overall survival by 6%.
- For patients undergoing chemotherapy the increase was less pronounced, but could not be excluded.
- Risks of ESAs must be balanced against benefits depending on the clinical circumstances of the individual patient.

- No conclusive evidence for effect modification by patient level characteristics (age, sex, Hb and Hct at baseline, Hb ceiling, type/stage of tumor) or study level characteristics (anticancer treatment, ESA treatment schedules, etc) for the outcomes tested.

Bohlius J, et al. Lancet, 2009; 273: 1532-1542

ESAs and survival in newly diagnosed MM patients





ESAs

No-ESAs

Multivariate analysis

ESAs: p=0.01 (HR for death: 1.5, 95% CI: 1.07-2.02)

Age: p<0.001 (HR: 1.032, 95% CI: 1.04-1.09)

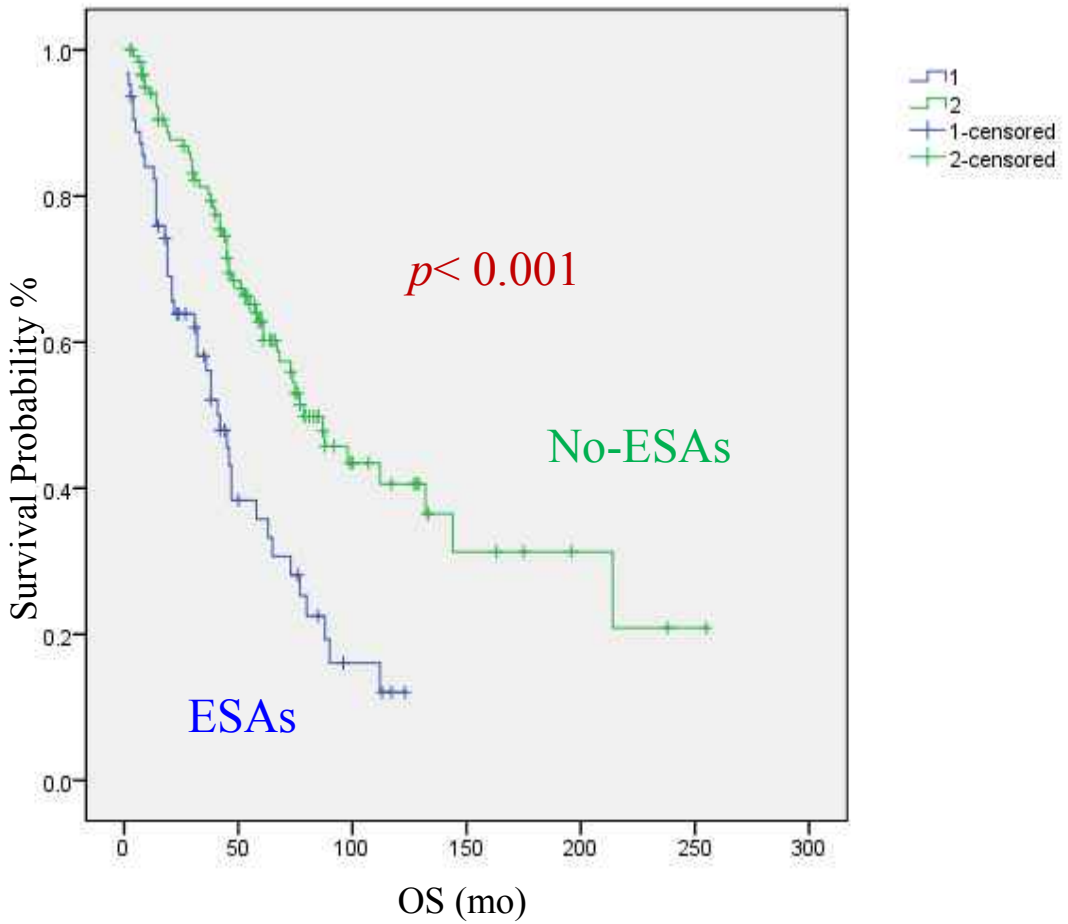
β2 M: p<0.001: (HR: 1.07 (95% CI: 1.04-1,09)

Median follow-up 76 (2-255)

Katodritou E, et al. Am J Hematol 2008; 83: 697-701

(2009 updated)

Survival according to ESAs administration (ISS I)



Overall survival

87mo (95% CI: 65-108)

vs

42mo (95% CI: 27-56)

Multivariate analysis

ESAs p<0.001 HR for death: 1.99 (95% CI: 1.12-3.5)

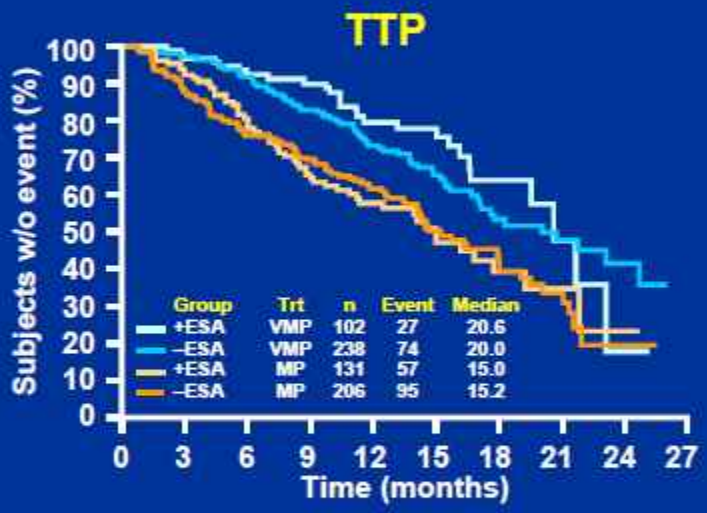
β2 M: p=0.03 HR: 1.09 (95% CI: 1.01-1.2)

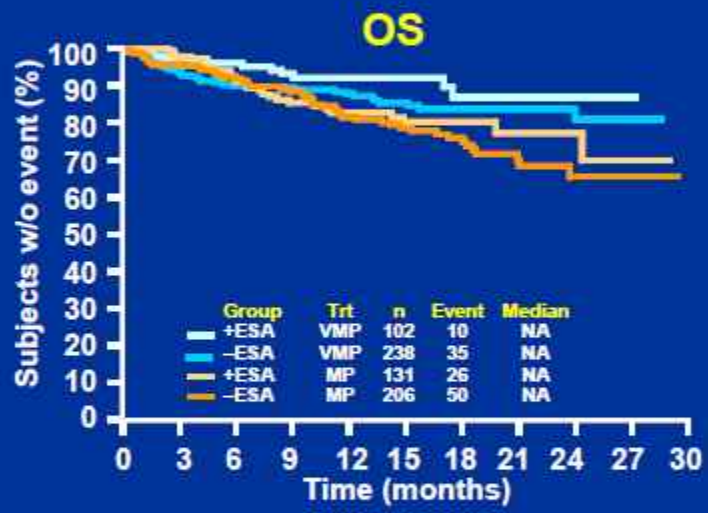
Progression-Free Survival (p=0.01)

ESAs arm: 24mo (95% CI: 16-32mo)

No-ESAs arm: 29mo (95% CI: 21-37mo)

ESA use did not adversely impact long-term outcomes with VMP or MP

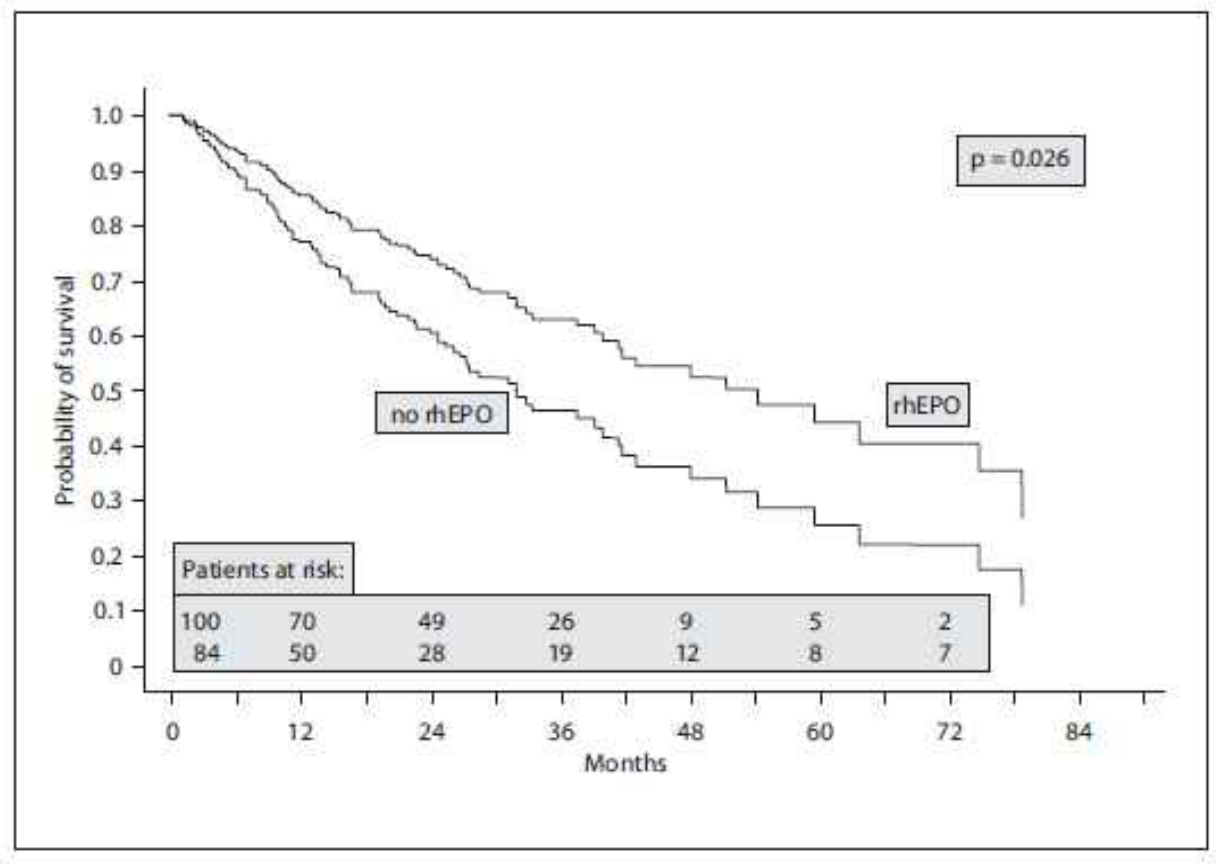




- Median TTP was similar regardless of ESA use in both arms
- 2-year survival rates appeared higher among patients receiving ESA

ESA can be safely administered with VMP/MP for the treatment of anemia in frontline MM patients

Richardson PG, et al. Blood, 2008;112: abstr 1741



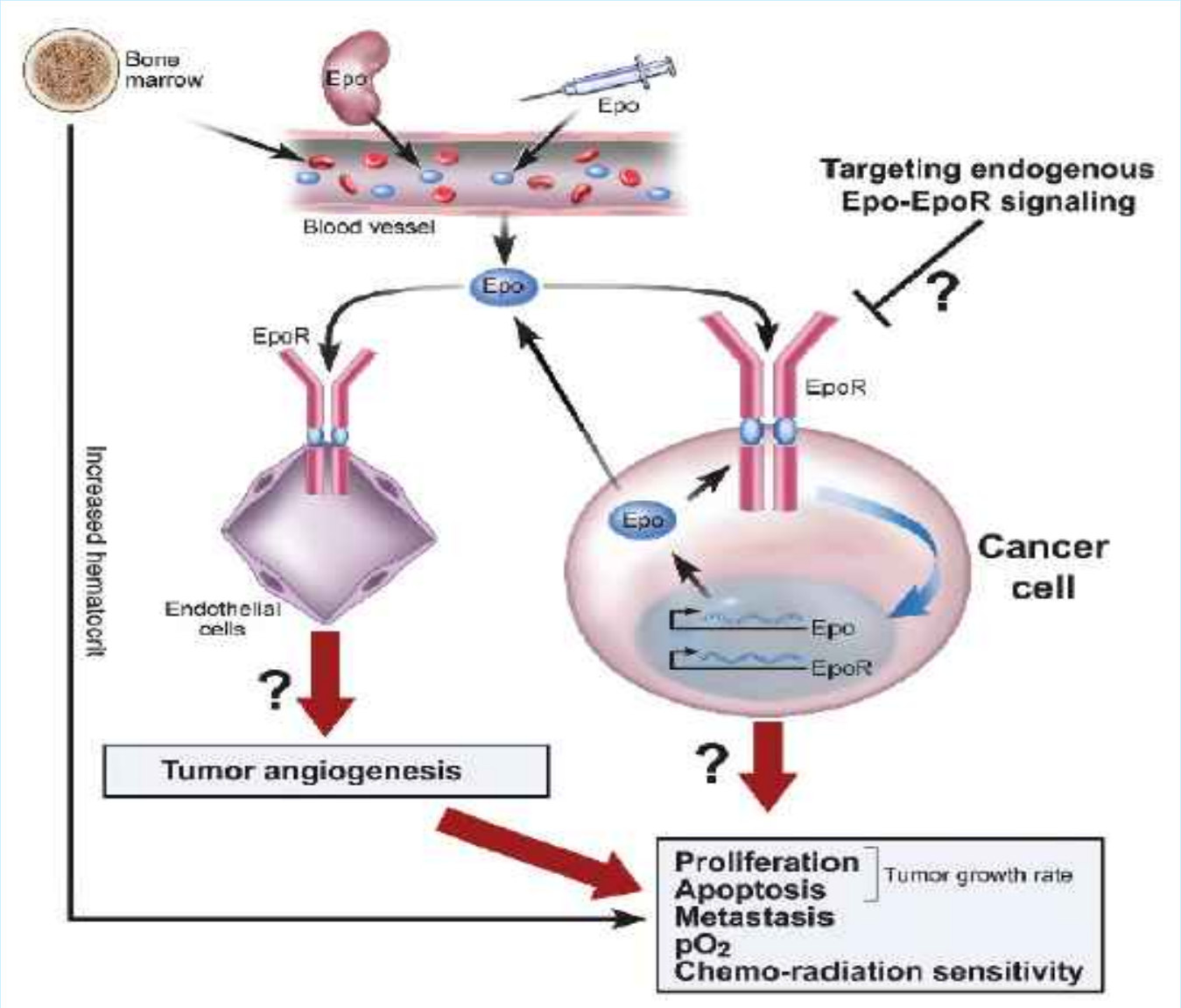
➢Adjusted survival for pts in SWOG stage II, III and IV (no difference in the unadjusted survival (p=0.4).

Baz R, et al. Acta Haematologica, 2007; 117: 162-167

- ✓Survival studies and meta-analyses have limitations (mixed populations, different settings, not comparable patients characteristics, magnification of the effects of some trials)
- ✓"No inferior survival" is not a sufficient end-point
- ✓A relatively long follow-up is required
- ✓Need for prospective studies to answer this query
- ✓Reasonable to avoid ESAs in newly diagnosed MM patients in whom physicians follow an "intention to cure" strategy

Katodritou E, et al. Cancer Treat Rev, online September 2, 2009
Glaspy J. Nat Rev Clin Oncol ,2009; 6: 500-502

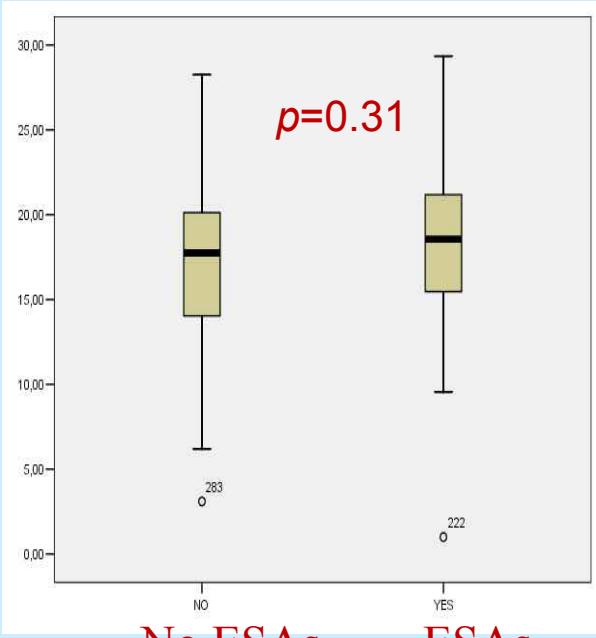
Possible mechanisms of ESAs-induced tumor promotion? Nothing has been proved!!



Hardee M, et al. Clin Cancer Res, 2006; 12: 332-339

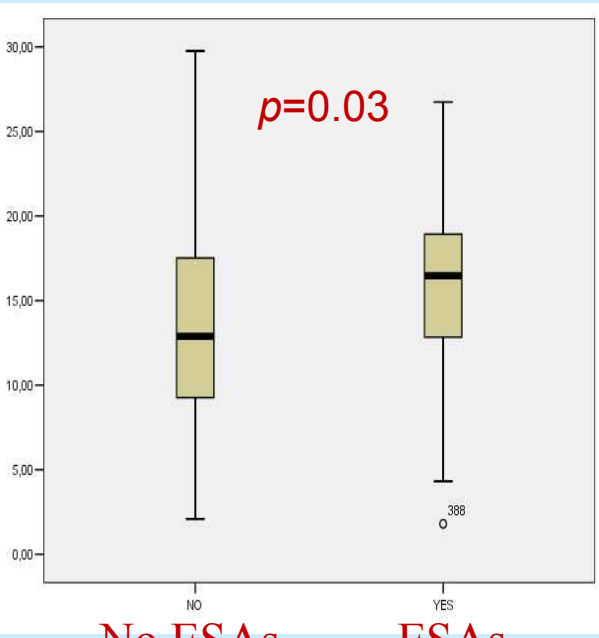
Bone marrow microvessel density (MVD) in 84 newly diagnosed MM patients on conventional treatment with or without ESAs administration

Baseline MVD



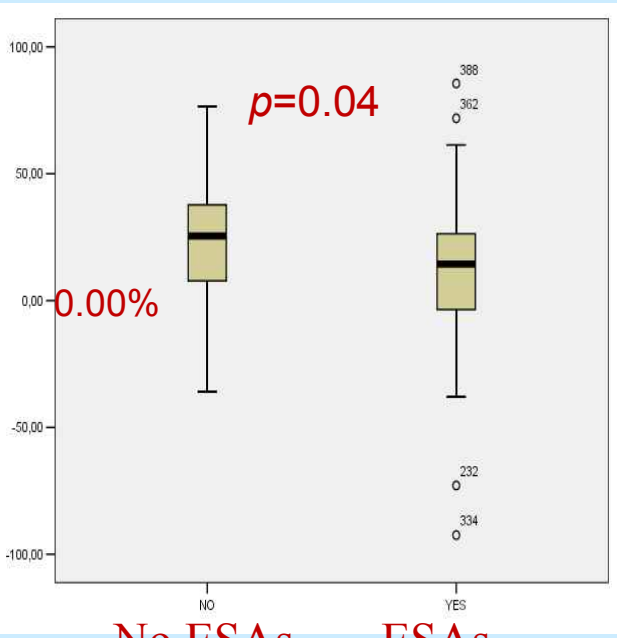
No ESAs ESAs

MVD at re-evaluation



No ESAs ESAs

% change of MVD



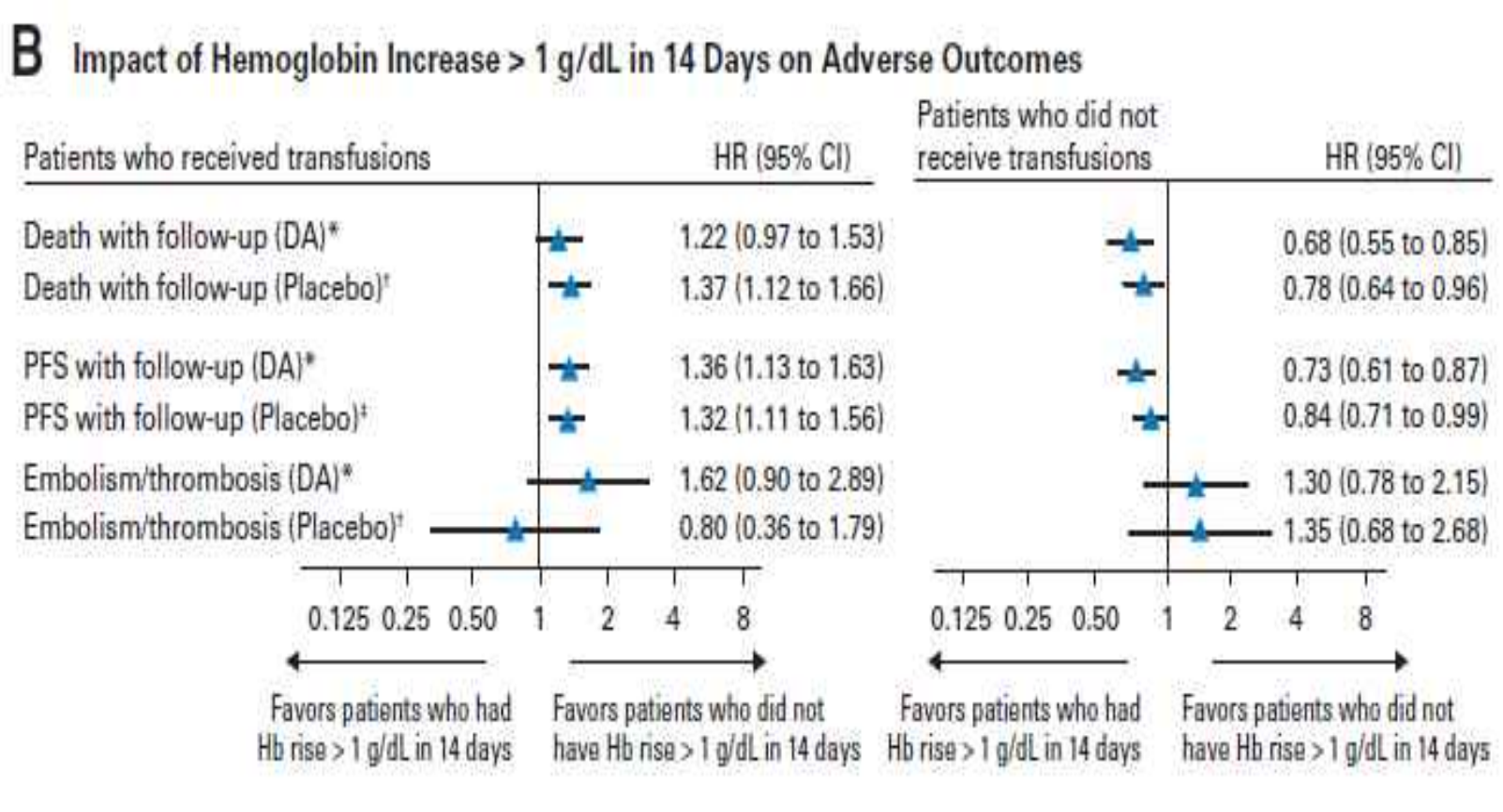
No ESAs ESAs

MVD increased in 15 pts (13/ESAs 2/noESAs) (p=0.03)

ESAs arm:14.5% (-410%-85.6%) CD34(+) microvessels/ mm^2
No ESAs arm: 24.9% (-36%-76.6 %CD34(+) microvessels/ mm^2

Katodritou E, Terpos E, et al. 2009, submitted

RBC transfusions



RBC transfusions and the rates of Hb increase owing to transfusions were associated with increased risk for disease progression and death

Ludwig et al, J Clin Oncol, 2009; 27: 2838-2847

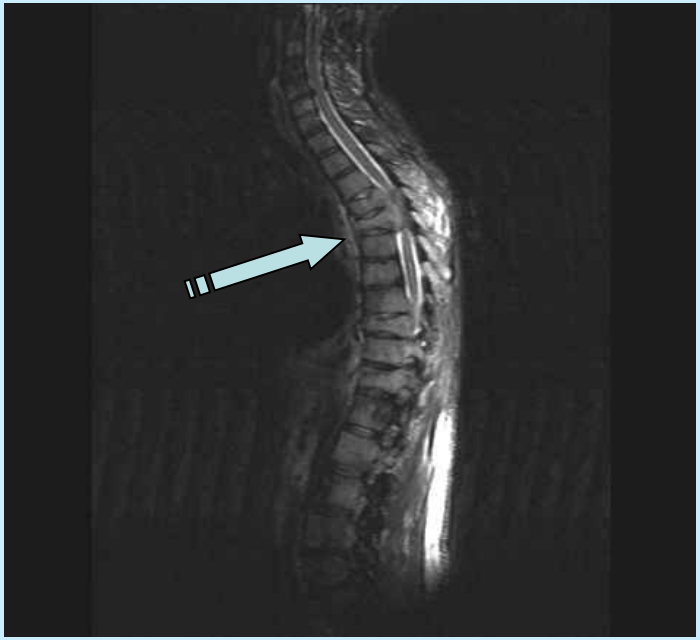
Conclusions

- Anemia is a frequent and serious adverse event in MM
- ESAs are established in the treatment of anemia in MM, however, their use should strictly follow the international guidelines
- IV iron supplementation improves response to ESAs, however, firm criteria of IRE are necessary (IV iron monotherapy under investigation)
- The need for predictors of response to ESAs and iron has not abated
- Hepcidin implication in the pathogenesis of MM needs further investigation
- ESAs should preferably be avoided if physicians follow an "intention to cure" strategy (novel agents, ABMT)
- RBC-transfusions is an acceptable therapeutic option, if used with caution

MANAGEMENT OF NEUROLOGICAL COMPLICATIONS IN MULTIPLE MYELOMA

Causes of polyneuropathy in myeloma:

- **Compressive**
  - Radiculopathy
  - Spinal cord compression
  - Base-of-skull tumors
- **Infiltrative**
  - Leptomeningeal infiltration
  - Numb chin syndrome
- **Autoimmune or inflammatory**
  - Peripheral neuropathy
- **Drug-related**
  - Peripheral neuropathy
- **Others**
  - Hypercalcemia, uremia
  - hyperviscosity
  - Diabetes Melitus, B12 insufficiency



Radiculopathy

Causes: Root compression, spinal cord or cauda equina compression due to: lytic bone lesions, vertebral plasmacytomas, foraminal stenosis (bone fracture)

- Symptoms: Back pain, root pain, weakness or paralysis of the lower extremities

- Diagnosis: MRI

- Action: if no spinal cord compression : corticosteroids and systemic treatment. In case of soft-tissue component causing the stenosis, radiation is beneficial.

Silberman J. & Lonial S. Hematol Oncol, 2008; 26: 55-65
Spinazze S, et al. Crit Rev Oncol Hematol, 2005; 56: 397-406
Dispenzieri A & Kyle RA. Best Prac & Res Haematol, 2005; 18: 673-688

Spinal cord compression

➢Usually involves thoracic cord (5% during the course of MM)

- Causes: extension of a myelomatous lesion to the extradural area

- Symptoms: back pain (radicular features), weakness, ataxia, spasticity, paraplegia

✓*Compression of the cauda equina:* pain in the buttocks, loss of sensation in the saddle area, weakness of the legs

- Diagnosis: MRI (CT scan?)

- Action: immediate administration of high-dose dexamethasone, radiation (4.000cGy fractionated over 4wks)

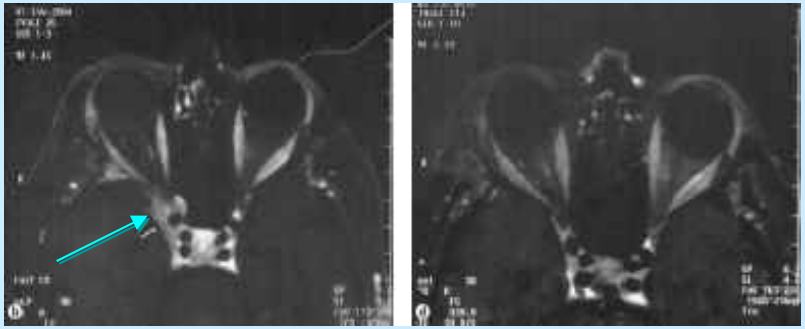
✓surgical decompression: beneficial if there is a pathologic compression fracture

Silberman J. & Lonial S. Hematol Oncol, 2008; 26: 55-65
Spinazze S, et al. Crit Rev Oncol Hematol, 2005; 56: 397-406
Dispenzieri A & Kyle RA. Best Prac & Res Haematol, 2005; 18: 673-688

Base-of-skull plasmacytomas

- Rare, usually occur during disease progression
  - Involvement of cranial nerves (e.g. 6th, 8th)
  - Numb chin syndrome: sensory disturbances (mental nerve or inferior alveolar nerve)
  - Lytic lesion in the mandible (10%): mandibular nerve
  - Orbital involvement: proptosis, visual loss occasionally

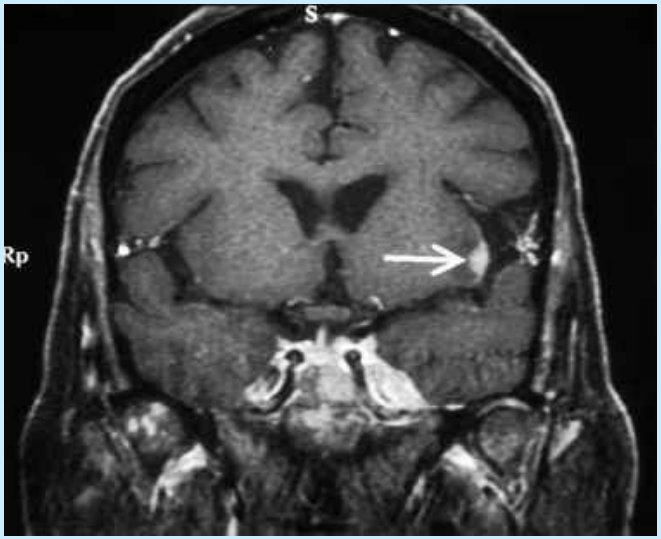
- Diagnosis: MRI (CT scan)
- Treatment: If anatomically suitable, surgery+radiation (50.000cGy), otherwise radiation+systemic therapy, gamma-knife radiosurgery (in case the tumor remnant is small), novel agents could be effective (limited data)

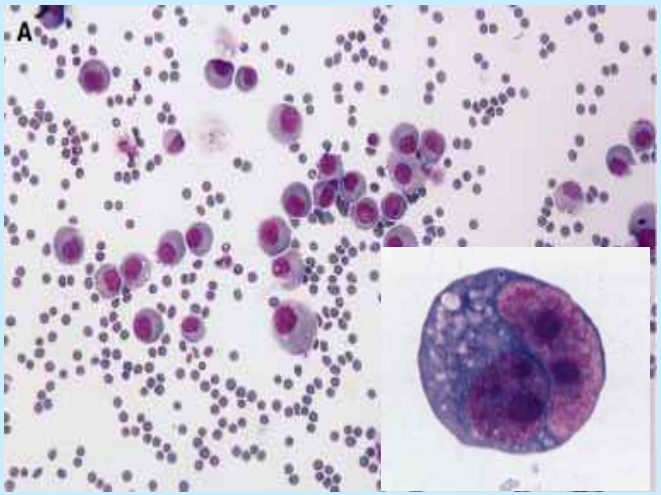


Dispenzieri A & Kyle RA. Best Prac & Res Haematol, 2005; 18: 673-688
Cerase A et al. Ann Hematol, 2008; 50: 665-674
Gozetti A et al. Clin Lymphoma Myeloma, 2007; 7: 376-378
Katodritou E et al. Acta Haematologica, 2007; 117: 20-23

Leptomeningial infiltration

- Uncommon (1%)
- focal weakness, lythargy, stupor, cranial nerve palsies, papillidema, CNS plasma cells





- Associated with:
  - Unfavorable cytogenetics
  - Plasmablastic morphology
  - High tumor mass
  - Extramedullary myeloma
  - Circulating plasma cells
  - Poor survival (<6-9mo)
- Treatment
  - Radiation
  - IT MTX, Ara-C

Fassas A, et al. Br J Haematol, 2002: 117: 103-108

Peripheral neuropathy (PN)

- Disease related
- Treatment related

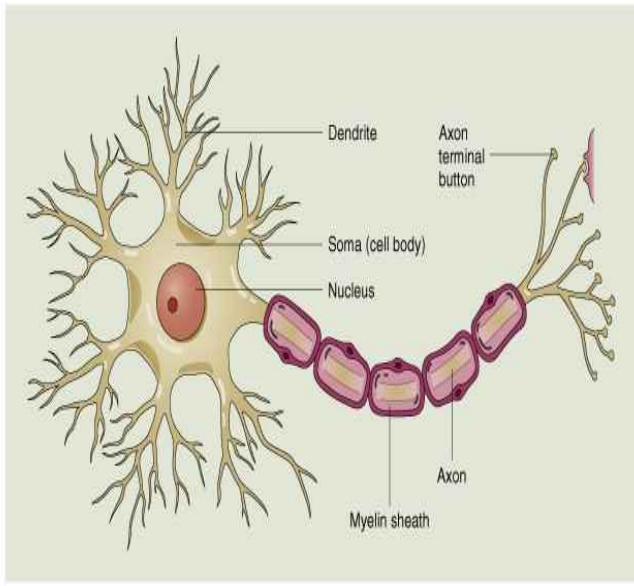
Symptoms of PN

- **Sensory**
  - decreased sensitivity: numbness
  - increased sensitivity: paraesthesia, hyperaesthesia
  - neuropathic pain
  - tremor
  - proprioceptive failure
- **Motor**
  - weakness
- **Autonomic**
  - hypotension
  - constipation, diarrhoea
  - bradycardia

Kelly JJ, et al. Rev Neurol Dis 2004;1:133-40

Peripheral neuropathy (PN) at diagnosis

- Routine clinical diagnosis: 3-13%
- Detailed neurological testing (FACT/EPS) :39-83% small fibres
- Histopathology: ~60%
- Axonal (EP), + demyelination (histology)
- Symmetric, distal, sensory or sensorimotor
- Most commonly in IgG myeloma
  M-component>3g/dL, κ light chain (65%)
- Mild in the absence of amyloidosis
- Light-chain deposition is often implicated
- EP does not predict the onset of clinical PN
- Refractory to any treatment



Silberman J & Lonial S. Hematol Oncol, 2008; 26: 55-65
Mileshkin L, et al. J Clin Oncol, 2006; 24: 4507-4514
Richardson PG, et al. J Clin Oncol, 2006; 24: 3113-3120
Richardson PG, et al. Blood, 2005; 106: abstr: 2548

Treatment-related PN in myeloma

- **Cytostatic drugs**[1]
  - **Vincristine**
  - **Cisplatin**

- **Novel agents**[2-11]**:**

  incidence according to disease status (newly diagnosed vs relapsed), dose, duration and predisposing factors

  ✓ ***IMiDs***[2-5]
  - **Thalidomide (27-75%**[3,4]**, grade ≥2 ≈ 30%**[2]**)**
  - **Lenalidomide (grade 3,4 <5%)**[5]

  ✓ ***Bortezomib***[6-11] **(21-64%**[6, 11]**, grade ≥3: 3-22%** [11, 8]**)**

1. Siberman J & Lonial S. Hematol Oncol, 2008; 26: 55-65
2. Mileshkin L et al. J Clin Oncol, 2006; 24: 4507-4514
3. Richardson PG, et al. May Clin Proc, 2004; 79: 875-882
4. Tosi P, et al. Eur J Haematol, 2005; 74: 212-216
5. Dimopoulos MA et al. N Eng J Med, 2007; 357: 2123-2132
6. Richardson PG, et al. J Clin Oncol, 2006; 24: 3113-3120 7.
7.Jagannath S, et al. Br J Haematol 2004;127:165-172
8. Badros A et al. Cancer, 2007; 110: 1042-1048
9. Richardson PG et al. N Eng J Med, 2005; 352: 2487-2498
10. San Miguel J, N Eng J Med, 2009; 359: 906-917
11. Richardson PG, et al. J Clin Oncol, 2009; 27: 3518-3525

How important is PN in myeloma?

- One of the most frequent non-hematological side-effects of myeloma treatment

- PN may have a serious impact on the patient's QoL
  - physical: discomfort, pain, decreased functioning
  - social
  - psychological

- "Frustrating" for the treating physician
  - prevention: difficult
  - treatment: disappointing

- Interference with treatment efficacy?
  - because of dose reduction
  - because of treatment interruption

Tariman JD, et al. Clin J Oncol Nursing 2008;12S3:29-36

Pathogenesis of treatment-related PN

➢ Main neurological targets

- **axon**
  - ✓ **large fibres: "dying back" axonopathy**
  - ✓ **small fibres (afferent fibres Aβ, Aδ, C, in bortezomib related PN)**
- **dorsal root ganglia (occasionally)**
- **Schwann cells (predominantly in bortezomib-related PN)**

➢ Potential mechanisms of damage

- **induction of apoptosis of neural cell bodies**
- **disruption of axonal transport**
- **damage to**
  - ✓ **endoplasmatic reticulum**
  - ✓ **mitochondria**
  - ✓ **vasa vasorum**

Murillo JR, et al. J of Pharm Pract 2008;21:138-45
Behin A, et al. Curr Opin Neurol 2008;21:534-9

Pathogenesis of thalidomide & bortezomib-induced PN

- **Thalidomide**[1]

  Down-regulation of TNF-α, NFκB-mediated inhibition of nerve-growth-factor mediated neuron survival

- **Bortezomib**[2]

  Mitochondrial- and ER-mediated dysregulation of Ca^{++} homeostasis[3], NFκB-mediated inhibition of nerve-growth-factor mediated neuron survival, auto-immune factors and inflammation, altered peripheral autonomic tone

- **Predisposing factors**[4-8]
  - **Advanced age**
  - **Previous exposure to neurotoxic antimyeloma agent**
  - **Pre-existing PN**
  - **Diabetes, alcohol abuse**

1. Cavaletti G, et al. Neurology 2004;62:2291-3
2. Argyriou AA, et al. Blood 2008;112:1593-9
3. Landowski TH, et al. Cancer Res 2005;65:3828-36
4. Richardson PG, et al. J Clin Oncol, 2006; 24: 3113-3120
5. Richardson PG, et al. Br J Haematol, 2009; 144: 895-903
6 Mateos MV, et al. Blood 2006; 108: 2165-2172
7. El-Cheikh J, et al. Clin Lymphoma Myeloma, 2008; 8: 146-152
8 Badros A, et al. Cancer, 2007; 110: 1042-1048

Clinical presentation of PN

		Thalidomide[1,2]	Bortezomib[3,4]
Localization	extremities: "glove and stocking"	yes	yes
	symmetrical	yes	yes
Sensory symptoms	paraesthesia	++	++
	numbness	++	+
	hyperaesthesia	+	++
	neuropathic pain	+	++
	proprioceptive failure	+	+
Motor symptoms	decreased muscle strength	+	+
Autonomic symptoms	hypotension, impotence, bradycardia	+	+

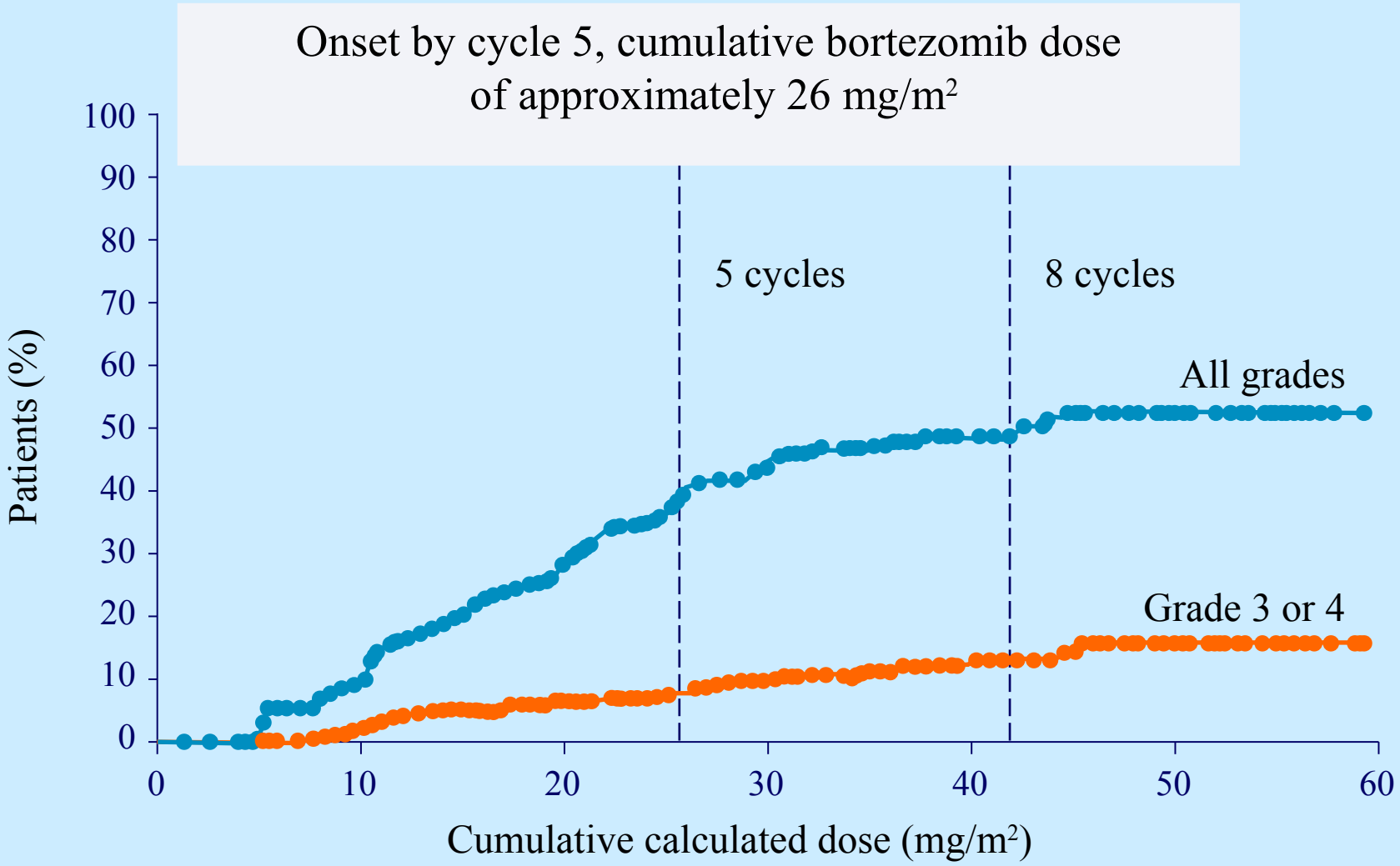
1. Chaudry V, et al. Neurology 2002;59:1872
2. Mileshkin L, Prince HM. Leuk Lymphoma 2006;47:2276-9
3. Argyriou AA, et al. Blood 2008;112:1593-9
4. Cata JP, et al. J Pain 2007;8:296-306

Evolution of PN

	Thalidomide	Bortezomib
Dose-dependent?	yes[1,2,5] correlation between total cumulative dose and clinical involvement (particularly if > 20 g administered)	yes CREST trial[3] (8% vs 15%) maximum at 30 mg/m^2 APEX trial[8] (cumulative dose 26mg/m^2)
Time-dependent?	yes slow onset (median ≅ 40wks) incidence doubles between 6 and 12 months (40% to 75%)[5,7]	yes slow or subacute onset maximum around cycle 5 followed by stabilization[8]
Need for discontinuation?	Yes 15-25%[5, 6]	Yes 5-34%[4, 8]
Reversible?	minimally	~70% have improvement or resolution 2−3 months[4,8]

1. Cavaletti G, et al. Neurology 2004;62:2291-4
2. Chaudhry V, et al. Neurology 2002;2002:1872
3. Jagannath S, et al. , Br J Haematol 2004;127:165-72
4. Richardson PG, et al. JCO 2006;24:3113-20
5. Mileshkin L, et al. JCO 2006;24:4507-14
6. Hulin C, et al. J Clin Oncol, 2009; 27: 3664-3670
7. Tosi P et al. Eur J Haematol, 2005; 74: 212-216
8 Richardson PG et al, Br J Haematol, 2009; 144: 895-903

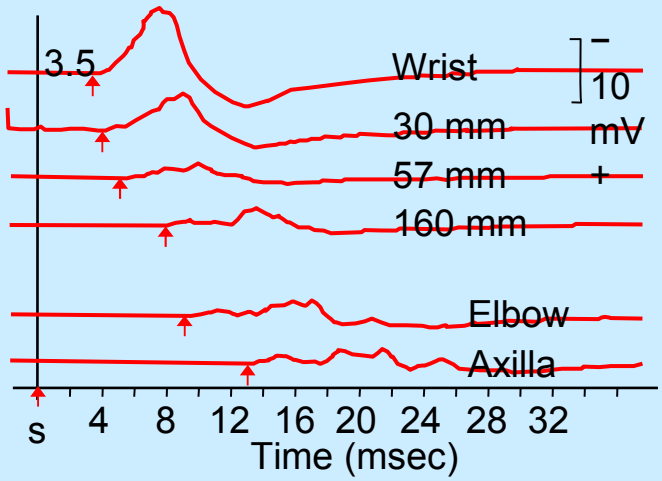
Risk of peripheral neuropathy with bortezomib increases over time



Richardson PG et al, Br J Haematol, 2009; 144: 895-903

Diagnosis of treatment-related PN

- **Clinical:** ask the right questions!
  - ✓ general: NCI CTC grading system
  - ✓ specific: Neurotoxicity FACT/Gynecologic Oncology Group
  - ✓ TNS (Total neuropathy score): combines symptoms, signs, abilty aspects and EP measures
  - ✓ Clinical neurological examination!
- **Electrophysiology:** nerve conduction studies, electromyography
  - ✓ sensory/motor
  - ✓ action potentials
  - ✓ conduction velocity
  - ✓ latency time
- **Imaging:** little value
- **Histology:** rarely required



Kelly JJ. Rev Neurol Dis 2004;1:133-40
Windebank AJ, Grishold W. J Peripher Nerv Syst 2008;13:27
Cavaletti G, et al. Neurology, 2003; 61: 1297-1300

Intervention for treatment-related PN

- **Prevention:** dose-modification guidelines (SmPC)

- Pharmacological treatment
  - ✓ vitamins: high doses of vitamins C and B6 can be toxic
  - ✓ nutritional supplements: glutamine, L-carnitine, α-lipoic acid
  - ✓ medication
    - tricyclic antidepressants: amitriptyline, nortriptyline
    - anticonvulsants: gabapentin, pregabalin
    - opioids: oxycodone, morphine, fentanyl
    - serotonin/norepinephrine-reuptake inhibitors
    - nonsteroidal anti-inflammatory drugs

- Topical treatment
  - ✓ lidocaine patch
  - ✓ capsaicin cream, cocoa butter
  - ✓ 0.5% menthol in calamine cream

- Others
  - ✓ high-dose intravenous gammaglobulins
  - ✓ physical exercise

Dose modification for PN: guidelines for thalidomide & bortezomib

Neuropathy	Action to be taken
Grade 1	continue to monitor the patient with clinical examination (or reduce the dose by 50% if symptoms worsen).However dose reduction is not necessarily followed by improvement of symptoms.
Grade 2	Reduce the dose and continue to monitor the patient - if no improvement or worsening: discontinue treatment - if the neuropathy resolves to grade 1 or better, treatment may be restarted if risk:benefit ratio is favourable
Grade 3	discontinue treatment
Grade 4	permanent discontinuation

Celgene. Thalidomide SmPC

Neuropathy	Action to be taken
Grade 1	no action
Grade 2, or grade 1 with pain	reduce bortezomib to 1.0 mg/m^2
Grade 3, or grade 2 with pain	withhold bortezomib until toxicity resolves then reinitiate at 0.7 mg/m^2 and administer once /wk
Grade 4	discontinue bortezomib

Janssen-Cilag. Bortezomib SmPC

Dose modifications do not adversely affect outcome

Richardson PG, et al. Br J Haematol, 2009; 144: 895-903

Intervention for treatment-related PN

- **Pharmacological treatment[1]**
  - **vitamins:** high doses of vitamins C and B6 may be toxic
  - **nutritional supplements:** glutamine, L-carnitine, α-lipoic acid
  - **medication**
    - ✓ tricyclic antidepressants: amitriptyline, nortriptyline
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    - ✓ opioids: oxycodone, morphine, fentanyl
    - ✓ serotonin/norepinephrine-reuptake inhibitors
    - ✓ nonsteroidal anti-inflammatory drugs

- **Topical treatment**
  - lidocaine patch
  - capsaicin cream, cocoa butter
  - 0.5% menthol in calamine cream[2]

- **Others**
  - high-dose IV IG[3]
  - physical exercise

1. *1. Argyriou AA, et al. Blood, 2008; 112: 1593=1599*
2. *2. Colvin LA, et al. JCO 2008;18:4519-20*
3. *3. Teoh G, et al. Blood 2006;108 (abstract 5097)*

Conclusions

- **Neurlogical complications in MM require clinical awareness**
- **Radiculopathy, spinal cord compression and base-of-skull plasmacytomas could be treated with: corticosteroids, systemic therapy radiation, surgery**
- **Treatment- related PN is a clinically frequent and important side-efffect, especially for patients receiving thalidomide and bortezomib**
- **PN has a serious impact on the QoL of MM patients**
- **Diagnosis relies predominantly on clinical follow-up**
- **Dose modification or interruption is more important than pharmacological intervention**

Future Prospectives

- More effective anti-myeloma agents: disease control
  - anemia improvement, decreased incidence of treatment- related anemia (novel agents), minimal need for ESAs or transfusions
  - agents targeting on biological pathways involved in the pathogenesis of anemia in MM (hepcidin)

- Novel agents with high efficacy and low neurotoxicity

Acknowledgements

Zervas K.

Dimopoulos M.A.

Terpos E.

Christakis J.

Kaloutsi V.

Verrou E.

Gastari V.

Greek Myeloma Study Group

Brugnara C.

Ganz T.

Westerman M.

Hedenus M.

Birgergard G.

Auerbach M.