



Induction treatment prior to autologous stem cell transplantation

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Newly diagnosed MM

Candidate for autologous stem cell transplantation

Yes

No

- Age ≤ 65 yrs
- Adequate organ function
- Lack of comorbidities

Treatment options for patients eligible for transplantation

Induction

↓

VAD

↓

Stem cell harvest
High-dose melphalan
Stem cell infusion

- Traditionally, VAD was considered standard induction treatment
- CR rate with VAD typically ≤ 10%

Reece. Hematology 2005;:353–359

Relevance of CR in MM

- CR is associated with prolonged PFS and OS¹
- Two meta-analyses of 21 studies enrolling 4990 patients who received ASCT, either single or double, provided demonstration of a significant relationship between maximal response (CR, nCR, VGPR) before and after ASCT and long-term outcomes (OS, PFS)
- CR is associated with good QoL²
- Important early treatment end point : achievement of CR

1 Van de Velde et al, *Haematologica* 2007
2 Ludwig et al. *IMW* 2007 (abs. PO-1103)

ASCT: new treatment paradigm with novel agents

- The novel agents
 - Thalidomide
 - Bortezomib
 - Lenalidomide

have been incorporated into newer induction regimens before ASCT in an attempt to increase the rate of CR as a way to furtherly improve outcomes (CR, PFS, OS) after ASCT

Thal-based regimens before ASCT: comparative studies

Regimen	N° pts	Response prior to ASCT (%)	Author
TD vs VAD	201	76 vs 52 No \neq ce in CR rate	Cavo et al <i>Blood</i> 2005
TD vs Dex	200	63 vs 41 No \neq ce in CR rate	Rajkumar et al <i>J Clin Oncol</i> 2006
TD vs VAD	204	≥ VGPR 35 vs 13	Macro et al ASH 2006 (abs. 57)
TAD vs VAD	402	72 vs 54 ≥ VGPR 32 vs 15	Lokhorst et al <i>Haematologica</i> 2008
CTD vs C-VAD	251	CR 19 vs 9 ≥ VGPR 39 vs 27	Morgan et al ASH 2007 (abs. 3593)

Thal-based regimens: response before and after ASCT

	TD vs VAD ¹	TAD vs VAD ²	CTD vs C-VAD ³
N° of pts	204	402	251
pre-ASCT ≥VGPR (%) CR (%)	35 vs 13 P = 0.002	33 vs 15 P<0.001 4 vs 2	39 vs 27 19 vs 9 P = 0.03
post-ASCT ≥VGPR (%) CR (%)	44 vs 42	49 vs 32 P<0.001 16 vs 11	67 vs 43 51 vs 40 P = 0.08
		EFS 33 vs 22 P < 0.001 OS 59 vs 62 P = 0.9	

1 Macro et al ASH 2006 (abs. 57) 2 Lokhorst et al IMW 2009 (abs 46) 3 Morgan et al ASH 2007 (abs. 3593)

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Bortezomib-based regimens before ASCT: phase III studies

Regimen	VD vs VAD		VTD vs TD		VTD vs TD		PAD vs VAD	
N° pts	(240)	(242)	(226)	(234)	(56)	(63)	(150)	(150)
N° cycles	4		3		6		4	
CR	6	1	21	6	30	6	5	1
≥ nCR	15	7	32	12	41	12	n/a	n/a
≥ VGPR	39	16	62	29	n/a	n/a	42	15
CR (P)	0.01		< 0.001		0.0006		< 0.001	
≥ nCR (P)	0.004		< 0.001		0.0006		< 0.001	
≥ VGPR (P)	< 0.0001		< 0.001		0.0006		< 0.001	

Harousseau J-L et al, ASH 2008 Rosinol L et al, ASH 2008 (abs. 654)
Cavo M et al, ASH 2008 (abs. 158) Sonneveld P et al, ASH 2008 (abs. 653)

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Bortezomib-based regimens before ASCT : response (≥ VGPR) by cytogenetic (FISH) abnormalities in phase III studies

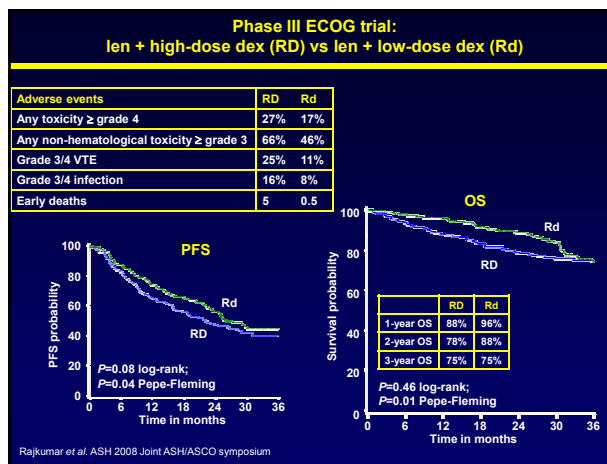
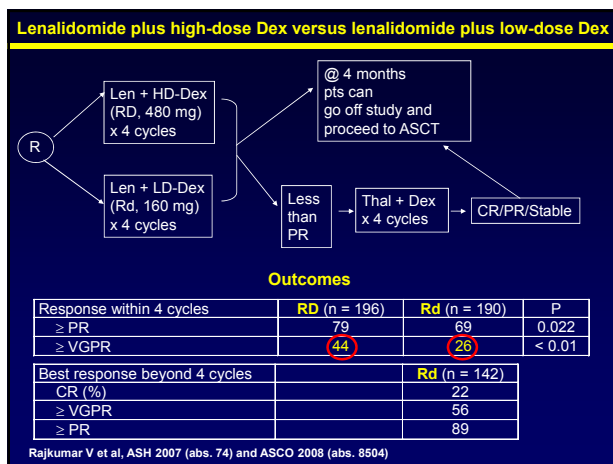
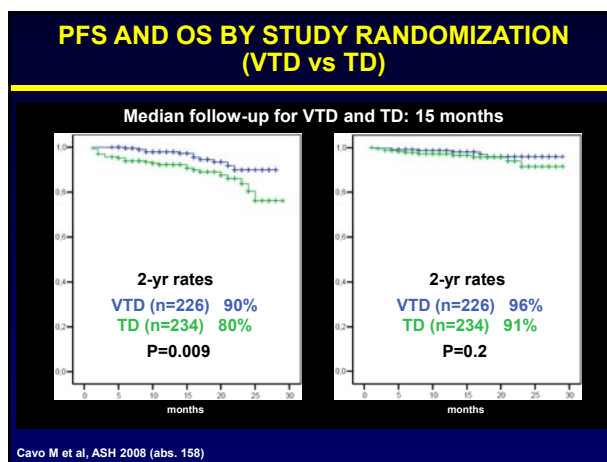
Regimen	VD vs VAD		VTD vs TD		VTD vs TD		PAD vs VAD	
N° Pts	(223)	(219)	(226)	(234)	(56)	(63)	(150)	(150)
del (13q)	47	15	73	25			64	48
t (4;14)	40	17	81	25.5	36	18*	52	29
del (17p)			73	6			n/a	
del (13q) (P)	< 0.001		< 0.001		0.03*		0.01	
t (4;14) (P)	0.04		< 0.001		0.03*		< 0.001	
del (17p) (P)	< 0.001		< 0.001		0.03*		< 0.001	

*CR comparison in pts with t(4;14), t(14;16) and del(17q)

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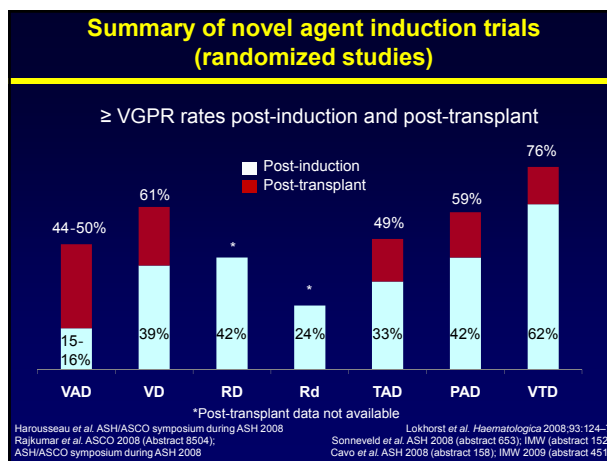
Bortezomib-based regimens in phase III studies: response before and after ASCT

Regimen N° Pts	VD vs VAD (223) (219)	VTD vs TD (226) (234)	VTD vs TD (56) (63)	PAD vs VAD (150) (150)
N° cycles	4	3	6	4
pre-ASCT				
CR	6 1	21 6	30 6	5 1
≥ nCR	15 7	32 12	41 12	n/a n/a
≥ VGPR	39 16	62 29	n/a n/a	42 15
post-ASCT				
CR	18 10	43 23	49 34	15 9
≥ nCR	37 19	55 32	64 53	n/a n/a
≥ VGPR	57 38	76 58	n/a n/a	59 50
post-ASCT (P)				
CR (P)	0.01	< 0.001	n/a	0.0015
≥ nCR (P)	< 0.0001	< 0.001	n/a	n/a
≥ VGPR (P)	0.0003	< 0.001	n/a	0.0019



Lenalidomide-based regimens: phase I/II studies

Regimen	N° pts	Response (4 cycles) (%)	Best response (%)	Author
RCd	53	≥VGPR 25	≥VGPR 32	Kumar et al ASH 2008 (abs. 91)
RVD	65	n/a	Median 9 cycles CR 26 nCR 18 VGPR 30 ≥VGPR 74	Richardson et al ASH 2008 (abs. 92)
VDCR	25	n/a	Median 6 cycles sCR 20 ≥CR 36 ≥VGPR 68	Kumar et al ASH 2008 (abs. 93)



Conclusions

- Novel agents incorporated in various combinations into newer induction regimens in preparation for ASCT effect
 - rapid
 - unprecedently high reduction in tumor cell mass
- High rates of CR/≥VGPR, up to the 30-60% range, have been reported with various induction regimens, more often within 60-80 days of treatment

Conclusions

- Although cross-trial comparisons are always difficult, it is likely that
 - the more effective partner of thal-dex is cyclophosphamide (CTD)
 - both bortezomib-dexamethasone (VD) and lenalidomide-HD dexamethasone (RD), but not lenalidomide-LD dexamethasone (Rd), effect comparable rates of major responses
 - a triplet bortezomib-based regimen, especially if including thalidomide (or lenalidomide?) as third active agent, results in the highest rate of major responses

Conclusions

- Major responses to bortezomib-based regimens are not adversely affected by cytogenetic abnormalities, including del (13q), del (17p), t(4;14) and t(14,16)
- 3-4 cycles of induction therapy with novel agents, especially if using a triplet combination, are the optimum treatment in preparation for ASCT
- Increasing the number of induction cycles up to 6 may furtherly, albeit slightly, improve the rate of major responses, but at the expense of increased toxicities

Conclusions

- Do increased rates of major responses (CR/≥VGPR) effected by novel induction regimens favorably influence post-ASCT outcomes?