Nové léky v indukční fázi u transplantovaných nemocných s MM

R.Hájek

Workshop CMG

Léčebné standardy v roce 2008 &

Organizace léčby MM v ČR

19.4.2008

Stávající stav

- U seniorů máme k dispozici thalidomid, bortezomib (Velcade) a lenalidomid (Revlimid) v relapsu onemocnění, v primoléčbě jen thalidomid.

- U juniorů stejně u relapsu, stejně v primoléčbě - na rozdíl od seniorů randomizované studie běží a většina z nich není uzavřena.

Jak nahradí indukční režim s novým lékem režim VAD před transplantací ?

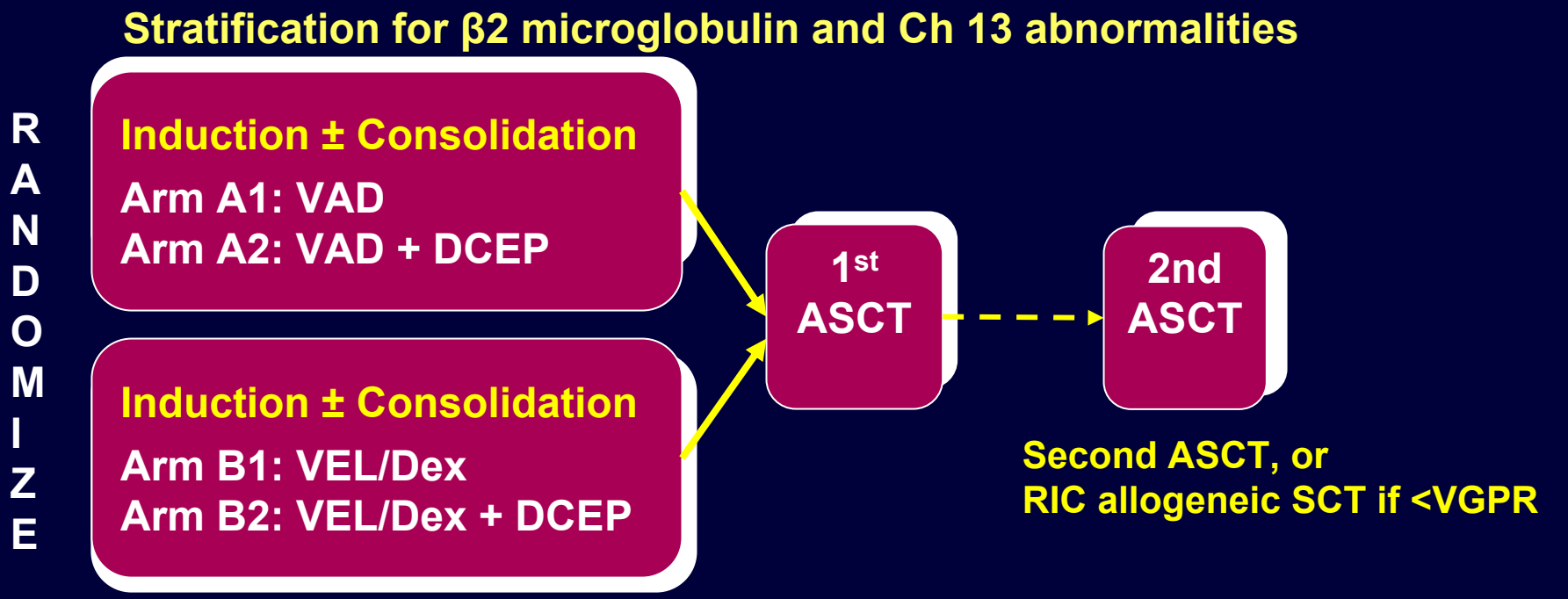
- TOXICITA (při VAD režimu jsme ztratili 20% nemocných)
- Specifická toxicita pro primoléčbu - trombózy, neuropatie
- Lze provést SBĚR krvetvorných buněk po indukci?
- Léčebná účinnost
- Jiné faktory
- Náklady

Bortezomib (Velcade)

Vel/Dex vs VAD Induction Prior to ASCT IFM 2005/01 Trial

Updated results: Randomized phase 3 IFM trial comparing Vel/Dex with VAD induction in MM up to the age of ≤ 65 years

- **Endpoints:** Primary include: CR^{IF-}+nCR post-induction; Secondary include: DCEP consolidation; Post-SCT outcomes, ORR, Safety
- **Patients:** 482 enrolled; previously untreated symptomatic MM with measurable paraprotein in serum/urine; age ≤65 years



Harousseau JL, et al. Ash 2007, abstract #450

Vel/Dex vs VAD

- **Induction and Consolidation**

VAD regimen (four 28-day cycles):

Vincristine 0.4mg/m^2 and doxorubicin 9mg/m^2, days 1–4
Dex 40mg, days 1–4 (cycles 1–4), and days 9–12, 17–20 (cycles 1–2 only)

Vel-Dex regimen (four 21-day cycles):

Bortezomib 1.3mg/m^2, days 1, 4, 8, and 11
Dex 40mg, days 1–4 (cycles 1–4), and days 9–12 (cycles 1–2 only)

DCEP regimen (two 28-day cycles):

Dex 40mg, days 1–4
Cyclophosphamide 15mg/m^2, etoposide 400mg/m^2, and cisplatin 10mg/m^2, days 1–4

- **Stem Cell Collection:**

Mobilization with G-CSF 10µg/kg for 6 days after cycle 3 of induction
If collection not adequate, second mobilization with cyclophosphamide 3g/m^2 and G-CSF 5µg/kg after cycle 4

Target collection: 5x10^6 CD34+ cells/kg, to enable double transplantation, if required

Harousseau JL, et al. Ash 2007, abstract #450

Vel/Dex vs VAD

Baseline Patient Demographics and Disease Characteristics

Characteristics	VAD (A1+A2) n=242	Vel/Dex (B1+B2) n=240
Median age, yrs	57.1	57.2
ISS stage III, %	22.3	21.7
β_2m > 3 mg/L, %	57.9	57.1
Del 13 by FISH, %	43	42
Median Hb, g/dL	10.8	10.9
Median Cr, umol/L	87	87

Harousseau JL, et al. Ash 2007, abstract #450

Vel/Dex vs VAD

▶Response* to Induction

Intention-to-Treat Analysis	VAD n=242	Vel/Dex n=240	P value
CR	3%	10%	0.0023
CR+nCR	8%	21%	<0.0001
≥ VGPR	**19%**	**47%**	<0.0001
≥ PR	**63%**	**80%**	**<0.0001**

▶Response* to Consolidation

Intention-to-Treat Analysis	No DCEP A1 + B1 n=242	DCEP A2 + B2 n=240	P value
CR	-	-	
CR+nCR	17%	19%	0.41
≥ VGPR	34%	38%	0.30
≥ PR	**71%**	**71%**	**0.93**

*modified EBMT criteria

Harousseau JL, et al. Ash 2007, abstract #450

Vel/Dex vs VAD

Impact of β_2M and Del (13q) on Post-Induction Response (CR + nCR)

	VAD	Vel-Dex	P value
β_2 M level > 3.0 mg/L	8% (n=140)	18% (n=137)	0.0101
≤ 3.0 mg/L	9% (n=102)	25% (n=103)	0.0018
Del 13q Deletion	10% (n=104)	26% (n=101)	0.0024
Normal/NE	7% (n=138)	18% (n=139)	0.0071

Harousseau JL, et al. Ash 2007, abstract #450

Vel/Dex vs VAD

Post-ASCT Response

Intention-to-Treat Analysis	VAD A1 + A2 n=242	Vel-Dex B1 + B2 n=240	P value
CR+nCR	24%	35%	0.0056
≥ VGPR	42%	62%	< 0.0001
≥ PR	**73%**	**80%**	**0.0463**

Actual SCT Performed	VAD A1 + A1 n=198	Vel-Dex B2 + B2 n=206	P value
CR+nCR	29%	41%	0.0089
≥ VGPR	51%	72%	< 0.0001
≥ PR	**89%**	**94%**	**0.14**

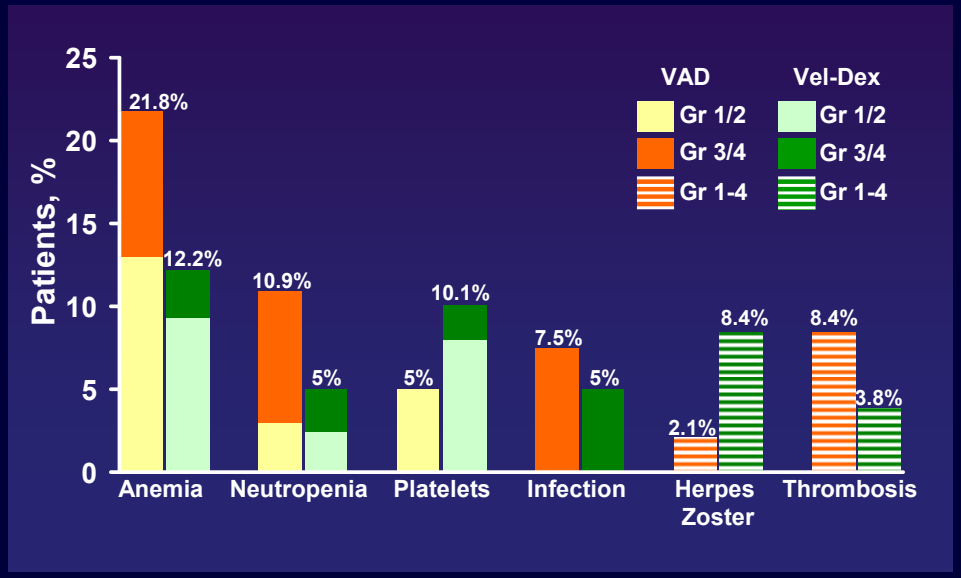
- **Median # of CD34+ ($x10^6$/kg)** — **VAD** (n=215) — **Vel-Dex** (n=224)
  - 1st mobilization — 8.50 — 6.75
  - 1 or 2 mobilization — 8.83 — 7.76

Vel-Dex arm stem cell collection yield was ≥ $2.1x10^6$ CD34+/kg in 97% of patients

Harousseau JL, et al. Ash 2007, abstract #450

Vel/Dex vs VAD

Hematologic Toxicity



Non-Hematologic Toxicity

All Grades	VAD n = 239	Vel/Dex n = 238
Fatigue	16.7%	21.4%
Rash	5.4%	10.1%
GI symptoms	25.9%	22.3%
PN	**22.6%**	**35.3%**
▪ Gr 2	6.7%	11.8%
▪ Gr 3-4	1.3%	6.3%

Harousseau JL, et al. Ash 2007, abstract #450

Vel/Dex vs VAD

- **Conclusion:**
  - Vel/Dex significantly improved post-induction response rate compared to VAD (ITT). DCEP consolidation did not significantly improve the outcome (ITT)
  - Post-induction CR with Vel/Dex translated into significantly better Post-SCT CR response rate In the Vel/Dex arm stem cell collection yield was ≥ $2.1x10^6$ CD34+/kg in 97% of patients
  - Vel/Dex regimen was well tolerated (18% grade 2-3 PN)

Harousseau JL, et al. Ash 2007, abstract #450

Bortezomib (Velcade)

- Velcade based indukční režim před AT má jasně lepší léčebnou odpověď než VAD (>90% ORR; > 70% CR+VGPR.
- Sběr štěpu bez problémů, asi nutný určitý odstup od posledního podání bortezomibu
- Toxicita je nižší celkově, i když je nutná profylaxe specifických toxicit (herpes)
- Profylaktický efekt proti trombózám je významný a u nově diagnostikovaných nemocných zásadní.

Thalidomid

TAD vs. VAD (HOVON-50/GMMG-HD3)

- **3x TAD vs. VAD as induction followed**
- **by MEL 200mg/m2 and PBSC support.**

- TAD significantly improved post-induction (72% vs. 54%; p< 0.001) RR compared to VAD
- Post-induction CR + VGPR (37% vs. 17%) with TAD translated into significantly better Post-SCT CR + VGPR response in TAD arm
- **49% vs. 32 % (p< 0.001)**

Lokhorst HM, et al. Haematologica 2008; 93, 124-127

TAD vs. VAD (HOVON-50/GMMG-HD3)

- **3x TAD vs. VAD as induction followed**
- **by MEL 200mg/m2 and PBSC support.**

- Stem cell collection - NO PROBLEM
  (4. cyklus CAD; interval)
- Drop out from protocol: 13% (VAD) vs. 18% (TAD)
- Toxicity: 62% pts. on TAD received full dose of Thal (400mg)
- Neuropathy 7% (VAD) vs. 12% (TAD)

Lokhorst HM, et al. Haematologica 2008; 93, 124-127

TAD vs. VAD (HOVON-50/GMMG-HD3)

- **Conclusion:**
  - TAD significantly improved post-induction response rate compared to VAD.
  - Post-induction CR with TAD translated into significantly better Post-SCT CR+VGPR response rate in TAD arm
  - Stem cell collection yield was succesful in 96% of patients
  - TAD was not tolerated as VAD if 400mg of thalidomide is target dose (12% grade 3-4 PN)

Lokhorst HM, et al. Haematologica 2008; 93, 124-127

Thalidomid

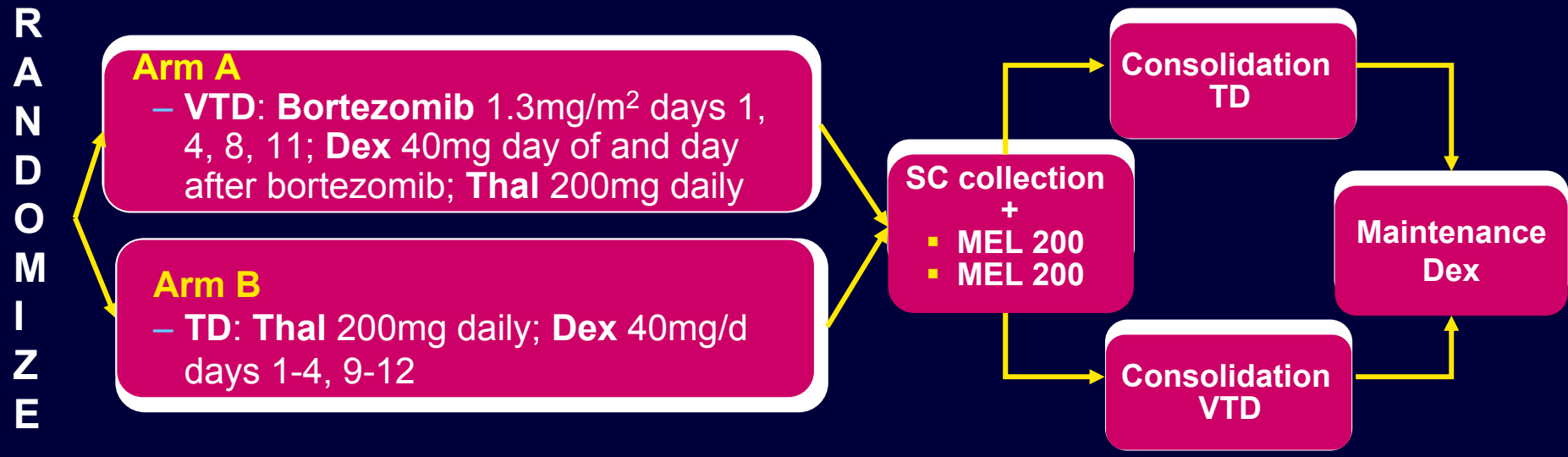
- Thal based indukční režim před AT má jasně lepší léčebnou odpověď než VAD (>80% ORR; asi 40% CR+VGPR.
- Sběr štěpu bez problémů, asi nutný určitý odstup od posledního podání thalidomidu
- Toxicita je daná výškou dávky thalidomidu 400mg je moc !
- Četnost neuropatie je podobná jako u VAD; je nezbytná profylaxe
- Kombinace antracyklinu s Thal a Dex je nejrizikovejsi z dostupnych

Thalidomid a bortezomib (Velcade)

VTD vs TD for SCT Induction

Phase III study: Planned interim analysis

- **Endpoints:** Primary include CR+nCR post-induction: Secondary include:CR+nCR post-consolidation, TTP, EFS, OS, Stem cell yield, and Safety
- **Patients:** 450 planned patients: 256 enrolled (Arm A n=129, Arm B n=127)
- **Dose:** Three 21-day cycles



– **DVT Prophylaxis:** Pts randomized to LMWH (enoxaparin 40mg/d), Aspirin (100mg/d), or wafarin 1.25mg/d

Cavo M, et al. ASH 2007, abstract #73

VTD vs TD for SCT Induction

Base-Line Patient Characteristics	VTD (n=129)	TD (n=127)
Median age yrs (range)	58 (34-66)	57 (29-65)
ISS (%) I II III	 47 34 19	 47 34 19
Median β_2-m mg/L (range)	2.9 (0.2-15)	3.0 (1.3-12)
Median albumin g/dL (range)	3.9 (0.38-17.3)	3.9 (1.3-59.9)
Median creatinine mg/dL (range)	1.0 (0.5-2.0)	1.0 (0.46-2.3)
Genetic abnormality Del13 pos (%) t(4;14) pos (%) Del17 pos (%)	 49 23 10	 44 19 8

Cavo M, et al. ASH 2007, abstract #73

VTD vs TD for SCT Induction

▶Response*	Induction			Post-SCT	
	VTD (n=129)	TD (n=127)	P value	VTD (n=74)	TD (n=79)
CR+nCR	**36%**	**9%**	<0.001	**57%**	**28%**
≥ VGPR	60%	27%	<0.001	77%	54%
< PR	7%	20%	0.003	-	-

*Modified EBMT criteria

– Cytogenetic abnormalities [Del 13q and t(4;14)] had no adverse impact on CR+nCR post-induction; a significantly improved CR+nCR rate with VTD was seen in these patients (Del 13q [P<0.001] and t(4;14) [P=0.002]) vs with TD

▶PBSC Harvest	VTD (n=112)	TD (n=108)	P-value
Median CD34+ cells (x10^6 /kg) (range) ≥ 4.0 x10^6 /kg (% pts)	9.2 (0-29) 94%	10.6 (0-37) 93%	NS
Median # of apheresis	1 (0-5)	2 (0-4)	NS

Cavo M, et al. ASH 2007, abstract #73

VTD vs TD for SCT Induction

▶Safety: Grade 3-4 AE (%)	VTD (n=129)	TD (n=127)	P-value
PN	**7**	2	**0.03**
Skin rash	**6.5**	1	**0.01**
Constipation	4	2	NS
Infection(s) [excluding HZ]	3	3	
DVT	**3**	**6.5**	**0.01**
Liver toxicity	2.5	3	NS
Vomiting/diarrhea	2	0	NS
Herpes Zoster infection	1	0	NS
Cardiac	0	2	NS
Other	9	10.5	NS

- Discontinuation due to toxicity: 3% VTD vs 2% TD
- Deaths due to toxicity: 0% VTD vs 1% TD
- **91% of pts received >90% of planned bortezomib administrations**

Cavo M, et al. ASH 2007, abstract #73

VTD vs TD for SCT Induction

Conclusions

- **VTD as primary therapy for MM significantly increased the rate of CR + nCR and ≥VGPR compared to TD and was not adversely influenced by t(4;14) or chromosome 13 deletion**
- Significant response benefit by VTD induction translated into a significantly higher probability of CR+nCR or ≥VGPR post-SCT
- Grade 3-4 AE, including SAE, was similar in the two treatment arms; Exception: higher rate of PN and rash with VTD, and higher rate DVT with TD
- Relatively low toxicity profile of VTD was reflected by: low discontinuation rate, high probability of receiving >90% planned dose, and absence of early deaths
- Primary therapy with VTD did not adversely impair the efficiency of PBSC harvest

Cavo M, et al. ASH 2007, abstract #73

Thalidomid a bortezomib (Velcade)

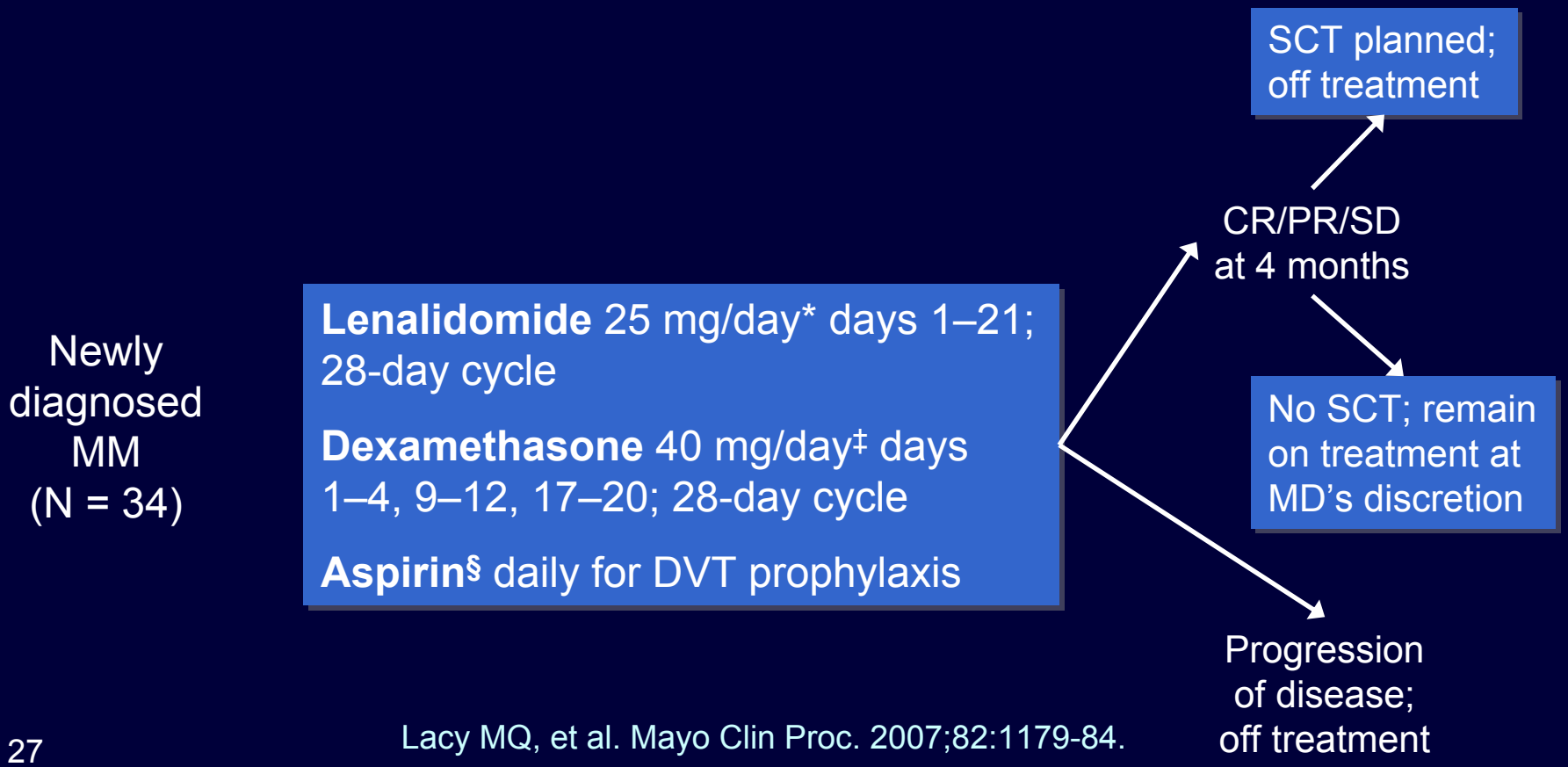
- Velcade zásadně zlepšuje účinnost režimu TD
- Sběr štěpu bez problémů, asi nutný určitý odstup od posledního podání
- Toxicita je daná kombinací obou léků
- Četnost neuropatie je vyšší a NÚ se umocňuje

- Kombinace V a T není v antracyklinu s Thal a Dex je nejrizikovější z dostupných

Revlimid

- Revlimid based indukční režim má léčebnou odpověď >80% ORR; asi 40% CR+VGPR.
- Málo dat !
- Sběr štěpu - málo dat. Existují i zprávy o potížích
- Toxicita - zásadní je neutropenie, trombogenní riziko podobné jako u Thal
- Četnost neuropatie je dáno dg. MM či lékem v kombinaci, ne lenalidomidem
- Další specifika - růstový faktor

Phase II trial of Len + Dex for newly diagnosed MM



Lacy MQ, et al. Mayo Clin Proc. 2007;82:1179-84.

Phase II trial of Len + Dex for newly diagnosed MM

EBMT response category	Patients responding, %* (n = 31)	No transplant, % (n = 21)
≥ PR	**91**	86
CR	**18**	24
VGPR or nCR	38	43
PR	35	19

Lacy MQ, et al. Mayo Clin Proc. 2007;82:1179-84.

Phase II trial of Len + Dex for newly diagnosed MM
grade 3 or 4 adverse events

Toxicita	%* (n = 31)
Fatigue	**21**
Neutropenia	**21**
DVT/pulmonary embolism	3

Lacy MQ, et al. Mayo Clin Proc. 2007;82:1179-84.

Jak nahradí indukční režim s novým lékem režim VAD před transplantací ?

- TOXICITA (při VAD režimu jsme ztratili 20% nemocných)
- Specifická toxicita pro primoléčbu - trombózy, neuropatie
- Lze provést SBĚR krvetvorných buněk po indukci?
- Léčebná účinnost
- Jiné faktory
- Náklady

Stávající stav

Lenalidomid (Revlimid)

Thalidomid

Bortezomib (Velcade)

- **TOXICITA (při VAD režimu jsme ztratili 20% nemocných)**
- **Specifická toxicita pro primoléčbu - trombózy, neuropatie**
- **Lze provést SBĚR krvetvorných buněk po indukci?**
- **Léčebná účinnost**
- **Jiné faktory, náklady**

Aktuální info o přípravě studie CMG 2008

Itálie-Austrálie- Višegrád

Low dose vs. high dose MELFALAN

400 pacientů během 2 letBortezomib (Velcade)

předpokládaný start: září 2008

Co - trial antikoagulační zrušen