Indication for DVT prophylaxis outline

Report of the International Myeloma Workshop Consensus Panel

Risk assessment model for management of venous thromboembolism in MM patients

Risk Factors	Univariate analysis *	
	OR	95% CI
Individual		
Obesity	0.98	0.96-1.00
Age	1.38	1.09-1.74
History of VTE and/or hypercoagulable state thrombophilia	2.5	1.40-4.46
Central–venous catheter or pacemaker	11.83	5.14-27.23
Disease-related:		
- Diabetes	NA	NA
- Chronic renal disease	3	1.19-7.56
- Infection	NA	NA
- Cardiac disease	1.57	1.18-2.08
- High degree and prolonged Immobilization	NA	NA
- Malignant neoplasm	7.67	4.69-12.53
Major Surgical procedures (including Vertebroplasty and Kyphoplasty) or trauma	15-20.5	6.07-37.09
Medications (Erythropoietin)	NA	NA
Blood clotting disorders	NA	NA
Myeloma-related		
- Diagnosis and hyperviscosity		
- Therapy : High dose dexamethasone,Doxorubicin, Multiagent Chemotherapy		

Abbreviations: CI, confidence interval; OR, odds ratio

*Heit JA, et al .Arch Intern Med 2000

Thrombotic risk assessment and action

HIGH RISK

At least one of the following risks:

- History of VTE and/or thrombophylia
- Cardiac disease
- Prolonged immobilization
- Major surgical procedures

- LMWH (enoxaparin 40 mg once daily)
  or
- Full dose warfarin (target INR 2-3)

STANDARD RISK

No previous mentioned risk factors

- Aspirine 81-325 mg once daily

Incidence of VTE in MM trial without prophylaxis

Treatment	Newly diagnosis VTE incidence (%)	References	Relapsed/ refractory VTE Incidence (%)	References
Melphalan-prednisone	2-8	Facon et al (2007). Hulin et al. (2009) Palumbo et al (2006) Ludwig et al (2011)	-	
Dexamethasone	3	Rajkumar et al. (2006)	-	
Thalidomide				
Single agent	4	Weber et al (2003)	2-3	Barlogie et al (2001). Kumar et al (2003)
Dexamethasone	17- 26	Rajkumar et al (2006)	2-8	Palumbo et al (2004)
Mephalan and prednisone	12- 20	Cavo et al (2004)	11	Anagnostopoulos et al (2003)
Doxorubicin combination	10-34	Facon et al (2007), Palumbo et al (2006)	58	Offidani et al (2004)
Cyclophosphamide	11	Zarvas et al (2004), Barlogie et al (2006)	7-8	Baz et al (2005)
		Wu et al (2006)		Garcia-Sanz et al (2004)
				Kropff et al (2008)
Lenalidomide				
Single agent	-		0	Richardson et al (2002)
High dose dexamethasone	26	Rajkumar et al (2010)	11-15	Dimopoulos et al (2007)
Low dose dexmethasone	12	Zonder et al (2006)	-	Weber et al (2007)
Cyclophosphamide	-	Rajkumar et al (2010)	14	Morgan et al (2007)
Bortezomib				
Melphalan and prednisone	1-5	San Miguel et al (2008).Palumbo et al (2010)	0	Palumbo et al (2007)
Dexamethasone	0	Harousseau et al (2006)	1	Richardson et al (2005)
Thalidomide and dexamethasone	3	Shen et al (2011)	-	Jagannath et al (2004)

Incidence of VTE in MM trial when thrombo-prophylaxis is used in regimens including thalidomide and lenalidomide

Treatment	Incidence of venous thromboembolism (%)				References
	Aspirin	LWMH	Low-dose warfarin	Full-dose Warfarin	
Thalidomide					
Thalidomide-dexamethasone	7		13-25	8	Niesvisky et al (2007), Cavo et al (2004), Weber et al (2003), Wang et al (2005)
Melphalan-prednisone-thalidomide		3-5			Baz et al (2005), Palumbo et al (2006)
Thalidomide multiagent chemotherapy, including anthracycline	18	5-24	14-31	8	Zangari et al (2004), Baz et al (2005), Minnema et al (2004), Offidani et al (2006), Barlogie et al (2006), Palumbo et al (2011)
Lenalidomide					
Lenalidomide-dexamethasone	3-14	2			Rajkumar et al (2005), Zonder et al (2006), Klein et al (2009)
Lenalidomide multiagent chemotherapy including anthracycline	6-9				Schey et al (2010), Baz et al (2006)

Risk of arterial thrombosis with 3 different therapies

Treatment	Thromboprophylaxis	Incidence of arterial thromboembolism (%)
Thalidomide, doxorubicin and dexamethasone (TAD)	Yes (LMWH)	4.5
Vincristinee, doxorubicin and dexamethasone (VAD)	No	6
Bortezomib, doxorubicin and dexamethasone (PAD)	No	6.4

Risk factor	Univariate analysis, HR (95% CI)	Multivariate analysis, HR (95% CI)
Factor VIII:C	1.92 (1.17-3.14)	1.85 (0.99-3.47)
Hypertension	3.70 (1.13-12.2)	11.7 (2.23-61.2)
Smoking	6.25 (1.61-24.2)	15.2 (1.78-130)

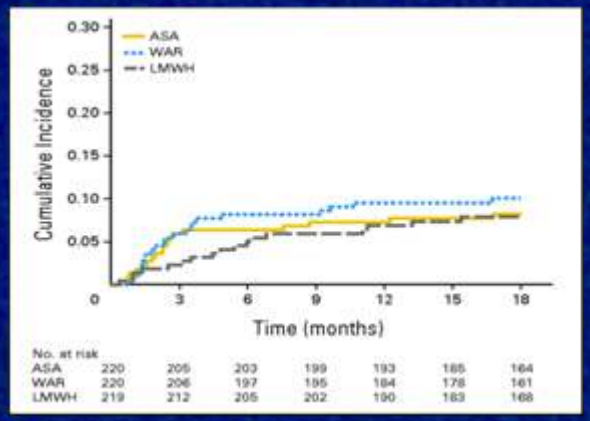
Libourel et al Blood 2010

Incidence of VTE in MM trial using consolidation/maintenance with thalidomide and lenalidomide

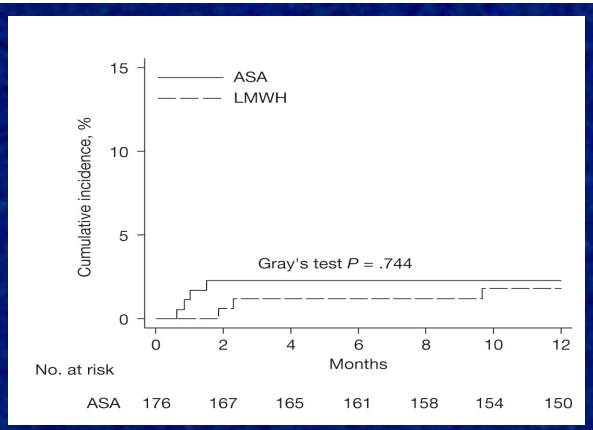
Treatment	N	Thromboprophylaxis	VTE incidence (%)	References
Thalidomide				
Consolidation/maintenance	314	NO	20 (6)	Barlogie et al.NEJM (2006)
+ pamidronate	201	NO	4 (2)	Attal et al. Blood (2006)
+ prednisone	114	NO	6 (5)	Spencer et al. JCO (2009)
+ dexamethasone	52	used Warfarin	0 (0)	Offidani et al BJH (2009)
+ interferon	64	not mandatory	2 (3)	Ludwig et al Haematologica (2010)
Lenalidomide				
Consolidation/maintenance (LP-L)	80	Aspirin	2 (2)	Palumbo et al JCO (2009)
Consolidation (L)	307	NA	1	Attal IFM trial 2005-02
Maintenance (L)	NA	NA	4 (1)	ASCO (2010) Mc Carthy et al ASH (2010)

VTE incidence in relation to time

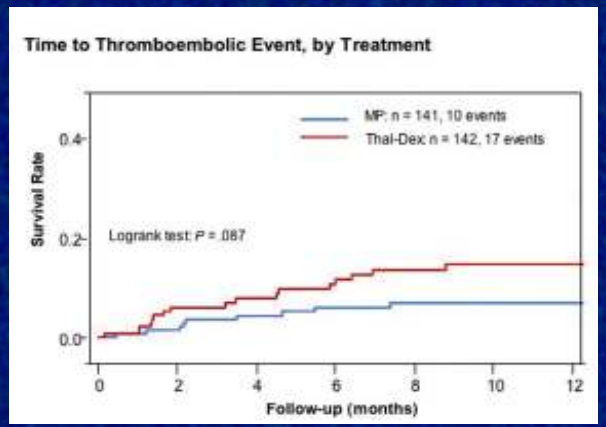
	VTE incidence (%) during the first 6 months	VTE incidence (%) in the entire follow-up
Thalidomide regimens [1] ASA (n=220) WAR (n=220) LMWH (n=210)	3.6 6.4 2.7	5.5 7.7 4.6
Lenalidomide plus low dose deaxamethasone [2] ASA (n=176) LMWH (n=166)	1 1	NA NA
Thalidomide plus dexamethasone [3] LMWH (n=145)	9	15



[1] *Palumbo et al JCO 2011*



[2] *Palumbo et al ASH 2010*



[3] *Ludwig et al Blood 2009*

Considerations

Risk of bleeding

- ASA should be withheld when platelets < 50 000/µL and the dose of the LMWH reduced.

- A 50% reduction in LMWH dose is recommended for patients platelets count < 50 000/µL, with LMWH treatment discontinued if platelets < 20 000/µl *(Kristinsson SY. Hematology Am Soc Hematol Educ Program 2010).*

Imaging tests and the use of D-dimer

- A landmark prospective cohort study monitored patients with serial ultrasound (6, 12, 24, and 36 months) after 3 months of anticoagulation for initial DVT. Veins were defined recanalized if they were < 2 mm on a single measurement or < 3 mm on two consecutive measurement (Prandoni P et al. Ann Intern Med 2002).
- Patients with persistently low D-dimer following a 3 to 6 months course of anticoagulation for idiopatic DVT may safely discontinue further anticoagulation with an acceptable risk of recurrent thromboembolic events. (Verhovsek M et al. Ann Intern Med 2008)

Conclusions

The cause of VTE is multi-factorial:

- **Individual**
- **Myeloma related**
- **Therapy related**

VTE decreases with thromboprophylaxis

In standard-risk patients → ASA

In high-risk patients → LMWH for 4-6 mo followed by ASA

During maintenance → ASA is not mandatory