Prospective assessment of clinical risk factors and biomarkers of hypercoagulability for the identification of newly diagnosed previously untreated patients with multiple myeloma at risk for cancer-associated thrombosis.

The observational ROADMAP-MM-CAT Study.

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INTRODUCTION

Research has focused on the implications of platelet, endothelial cell and blood coagulation activation in the risk of venous thromboembolism (VTE) in patients with multiple myeloma (MM). This common complication in the newly diagnosed MM (NDMM) patients remains high despite guideline-based thromboprophylaxis use. We aimed to explore cellular and plasma hypercoagulability in NDMM patients to identify relevant biomarkers that can be used in combination with clinical factors in the development of a risk assessment model (RAM) for VTE.

PATIENTS –METHODS

The study was prospective non-interventional trial and newly diagnosed patients with MM (n=144) were enrolled. At enrollment a standardized clinical research form was completed to include disease characteristics and relevant VTE risk factors. Patients were followed up for 12 months. The primary endpoint was symptomatic objectively confirmed VTE. Patients were risk stratified and received thromboprophylaxis (none, aspirin on low molecular weight heparin (LMWH) based on previously published recommendations by the IMWG and EMN. Prior to treatment initiation and thromboprophylaxis initiation baseline biomarkers were obtained: procoagulant phospholipid-dependent clotting time (Procoag-PPL®), fibrin monomers (FM), D-Dimers, thrombomodulin activity (TMA), activated factor VII (FVIIa), tissue factor activity (TFa), factor V (FV) and antithrombin (AT), plasma levels of P-Selectin and heparanase and thrombin generation. These were compared against previously measured values in a population of healthy individuals (n=30).

Follow up and VTE:

- Rate of symptomatic VTE during follow up was 10.4%.
- 9/15 (60%) occurred within 3 months from treatment initiation
- 6 were not on any thromboprophylaxis.; 6 patients were on aspirin at the time of the event and 3 were on LMWH.
- VTE rate did not differ significantly between patients who received thromboprophylaxis and those who did not.
- The rate of VTE was not significantly different between patients who received IMiD-based (11.4%) treatment and patients on other therapy (10%)

Patients' clinical characteristics	
Age (years)	66.0±2.0 (36-86)
Male/female	76/68 (53%/47%)
BSA (m ²)	1.85±0.20 (1.46-2.50)
ISS stage - n (%)	
I	46 (32%)
II	33 (23%)
III	65 (45%)
Anti-myeloma treatment - n (%)	
Pi-based	92 (64%)
IMiD-based	46 (32%)
Other	6 (4%)
Dialysis at diagnosis - n (%)	14 (10%)
Bone disease present - n (%)	102 (71%)
High risk cytogenetics - n (%)	27 (19%)
Comorbidities and VTE risk factors non related with the cancer - n (%)	
Active pulmonary disease	13 (9%)
CV risk factors	110 (76.4%)
Thromboprophylaxis after enrollment in the study - n (%)	
None	47 (33)
Aspirin	74 (51.0)
LMWH (tinzaparin)	23 (16)

RESULTS

Risk factors for VTE:

Univariate:

Clinical and disease predictors:

- Pulmonary disease was significantly associated with the occurrence of symptomatic VTE (OR 4.85, 95% CI: 1.28 – 18.33; p = 0.020).
- M-peak in gr/dl prior to treatment initiation was inversely associated with symptomatic VTE (OR = 0.72, 95% CI: 0.53 – 0.97; p=0.032).

Biomarkers and VTE:

- The patients with Procoag-PPL® ≥46.9 have a 3.49 times higher risk of VTE compared to patients with Procoag-PPL® <46.9 sec (OR=3.49, 95% CI: 1.13-10.82, p=0.030).
- Patients with ETP ≥ 1087.43 nMxmin versus patients with ETP < 1087.43 nMxmin had significantly lower risk of VTE (OR =0.25 95% CI 0.07-0.83, p=0.024).
- Patients with TFPI ≥39.08 versus patients with TFPI <39.08 had a 7.75 higher risk of VTE (OR=7.74 95% CI 1.51-39.70, p=0.014).

Multivariate analysis:

The presence of pulmonary disease (OR 18.06 95% CI 2.88-113.08, p=0.002), Procoag-PPL® ≥46.9 versus <46.9 sec (OR 3.18 95% CI 0.88-11.45, p=0.076), ETP <1087.43 nMxmin versus ≥1087.43 nMxmin (OR 4.81 95% CI 1.19-19.48, p=0.028) and Mpeak decrease by 1g/dl (OR 0.64 95% CI 0.46-0.89, p=0.008) were all independently associated with VTE occurrence.

This multivariate logistic regression model corresponded to the following equation:

$$\log(\text{odds for VTE}) = -3.16 + (2.89 * \text{pulmonary disease}) + (1.16 * \text{Procoag-PPL}_{\text{binary}}) + (1.57 * \text{ETP}_{\text{binary}}) - (0.45 * \text{Mpeak})$$

A score of 1 for presence of pulmonary disease, 1 for Procoag-PPL® ≥46.9, and 1 for ETP <1087.43 nMxmin, or 0 for absence of pulmonary disease, Procoag-PPL® <46.9 sec, and ETP ≥1087.43 nMxmin respectively, whereas Mpeak was treated as a continuous variable (in g/dl). Patients were stratified at high or intermediate/low risk group:

- 2.2% VTE rate in the intermediate/low risk group
- 25% VTE rate in the high risk group.

CONCLUSION

NDMM remain at risk of VTE despite recommendation-based risk stratification. Patients show biological signs of hypercoagulability related with platelet exhaustion. Pulmonary disease, lower M peak and longer Procoag-PPL® and lower ETP all independently predict VTE and can be prospectively incorporated into a RAM for VTE in multiple myeloma.

Profile of hypercoagulability at diagnosis of MM prior to treatment initiation compared to healthy subjects.

	Healthy subjects (n=30)	MM (n=144)	p
Cellular derived hypercoagulability			
Procoag-PPL (sec)	62.8±8.6	45.6±22.6	<0.0001
TFa (ng/ml)	0.26±0.13	3.97±3.10	<0.0001
Heparanase (ng/ml)	0.13±0.03	0.34±0.52	0.476
P-selectin (ng/ml)	62660.3±1039	38122.1±31	<0.0001
Blood coagulation factors and natural inhibitors			
FVIIa (ng/ml)	50.9±10.6	74.1±147.6	0.022
In vivo fibrin formation/lysis			
D-Dimers (µg/ml)	0.31±0.08	1.80±3.41	<0.0001
Thrombogram parameters			
Lag-time (min)	2.53±0.43	4.20±2.16	<0.0001
ttPeak (min)	5.28±0.73	7.33±2.76	<0.0001
Peak (nM)	287.8±35.7	214.4±80.1	<0.0001
MRI (nM/min)	109.9±24.5	80.2±45.7	<0.0001
ETP (nMxmin)	1496.8±191.4	1181.8±398.4	<0.0001