

Haemostasis disorders in multiple myeloma

There is a double risk of haemostasis disorders in multiple myeloma: firstly, a risk of venous thrombosis and secondly, a haemorrhagic risk, both are of multi-factorial origin.

These risks (which are patient dependent risks (basal area), with a context of tumour and myeloma of specific mechanisms) are due to the monoclonal protein, to myelomatous cells and to treatment. New therapeutic agents are linked to either a raised thrombotic risk (IMiDs: Thalidomide and Lenalidomide), or a haemorrhagic risk (Bortezomib). This is where the difficulties in prevention and treatment arise.

Thrombotic side: VTE and multiple myeloma

In cancers, deep vein thrombosis (DVT) is the 2nd cause of death, with the 1st being idiopathic venous thrombosis, the relative risk of cancer is multiplied by 3 to 7 in 2 years, depending on the type and the age of the tumour.

The incidence of occurrence of venous thromboembolic events is, in cases of monoclonal gammopathy of undetermined significance (MGUS), 0.9/1000 and 3.1/1000 in multiple myeloma cases. As in all cancers, the risk is major in the first year following diagnosis:

RR = 8.4 (CI 95 % 5.7 - 12.2) in MGUS and RR = 11.6 (CI 95 % 9.2 - 14.5) in MM.

Thrombosis disease is principally venous thrombosis in the lower limbs (left > right), pulmonary embolisms (PE), venous thrombosis of the upper limbs (< 5% of DVT) or of atypical location (VT of the vena cava); IVDCs are rare.

Thrombogenic mechanisms

1. Patient risk factors (RFs)

Age > 40 years, obesity, evolving cancer, congenital thrombophilia etc.

2. Tumour disposition: permanent hypercoagulability state

The release of procoagulant molecules from the tumour cells, cellular interaction dysfunctions between tumour cells and endothelium or platelet cells, and the circulating micro particles rich in tissue factor (TF) and phospholipids (PL), contributing to the hypercoagulability state.

3. Prothrombotic state caused by myeloma

Resulting from the effects of the monoclonal protein (total Ig or free light chains): hyperviscosity, interaction with fibrinolysis, autoantibody activity and myelomatous cell effects.

Effects caused by the monoclonal protein

1 Hyperviscosity

The hyperviscosity syndrome arises if IgM > 40 g/l; IgG > 50 g/l; IgA > 70 g/l with a frequency of approximately 6%. Suggestive symptoms include an alteration in the general state, neurological signs (nausea, dizziness, paraesthesia and vision disorders) and vascular signs (epistaxis, skin haemorrhages, retinal occlusion and vascular thrombosis). It is an oncological emergency of poor prognosis as there is a risk of multiple organ failure.

2 Hypofibrinolysis and fibrinof ormation anomalies (63 - 73% of MM)

The monoclonal protein interferes with fibrin polymerisation; the fibrin clot constituted is abnormal and persists as it is poorly recognised by the fibrinolysis factors.

3 Autoantibody activity

This is non specific (lupus-anticoagulant like, IgG kappa and IgM lambda, light chains) or specific (anti-protein S, anti-protein C, but no anti-thrombin autoantibodies have been described to date).

Effects caused by myelomatous cells

The myelomatous plasma cells that release IL6 activate the promoter of the coding genes of the inflammatory and procoagulant molecules: fibrinogen, CRP, FVIII, VWF, TF and PAI-1.

Furthermore, 9 - 23 % of patients with MM develop an acquired resistance to activated protein C (APC) (FV Leiden mutation absent) whereby the mechanisms are: an increase in FVIII, a decrease in PS and/or PC, TFPI and thrombomodulin (TM) amplified by the IMiDs: Thalidomide and Lenalidomide (too many factors to destroy for the APC, hence a resistance to APC).

4. Anti-tumour chemotherapy

The overall thrombotic risk caused by the anti-cancer chemotherapy is correlated to the doses and the treatment period. The incidence of DVT while undergoing treatment for MM is < 5 % in cases of conventional chemotherapy or IMiDs monotherapy treatment; it is however raised in the case of combined treatment with IMiDs and dexamethasone (8 - 26 %), or IMiD and a classic chemotherapy (17 - 58 %). Bortezomib (Velcade®) does not cause any thrombotic risk.

The thrombotic risk of IMiDs is especially raised in the first year of treatment (peak of incidence in the first 60 days; 80 % of DVT occurs in the first 6 months) and this risk is raised yet further still in newly diagnosed myelomas. It is not enhanced by the fitting of a catheter as the medication is administered per os. The mechanisms are an increase of the thrombin generation, Willebrand factor and the TF activity. Genetic polymorphisms (SNP) have been associated with an increase in the risk of DVT: CHEK1, XRRC5, LIG1, ERCC6, NFKB1, TNFRSF17, CASP3.

Treatment and prevention of VTE (venous thrombo-embolism) during MM

There is no consensus, just a number of good practise recommendations (AFSSAPS (French Health Products Safety Agency) Nov 2009, guide "Multiple myeloma" HAS (French National Authority for Health) Dec 2010, Chest etc.).

Prevention while taking IMiDs is not routine in the case of monotherapy, but becomes so if IMiDs are combined with:

- **Thalidomide:** LMWH (first 6 months: doses to be adapted in patients suffering from renal insufficiency) then aspirin (80 - 100 mg/day),
- **Lenalidomide:** LMWH or aspirin from the outset.

While taking IMiDs, estrogen and progestin oral contraceptives (contraceptives or HRT for the menopause) must be avoided; in the case of combined therapy with EPO, this must be stopped if the Hb is > 12 g/dl (majoration of the thrombotic risk).

Haemorrhagic side

The frequency of haemorrhages during MM varies according to different studies (from 7 - 33 %) and according to the type of monoclonal immunoglobulin (Ig): IgG (15 % of patients have a haemorrhagic tendency), IgA (40 %), IgM (60 %), IgD (myeloma is very rare but the haemorrhagic risk is +++). Death occurs in 3 % of cases by massive haemorrhaging. The haemorrhages are mainly mucocutaneous or cerebral/retinal.

Haemorrhagic mechanisms

They are multi factorial and self-enhancing:

- **Patient RFs:** acquired (antiplatelet drug? Renal insufficiency? Hepatic pathology?) or constitutional (hereditary coagulation diseases? Previously unexplained haemorrhagic tendency?)
- **RFs in regards to the tumour:** thrombophilia by medullary invasion. Thrombopenias are observed in 6 - 15 % of cases of MM at the diagnosis; they are generally moderate (50 - 100 G/l) and respond well to corticoids.
- **RFs of MM:**
 - *Hyperviscosity syndrome:* due to monoclonal Ig can cause bleeding. It is mainly the haemorrhages of the micro vessels (buccal, genital, gastro-intestinal, retinal and epistaxis) whereby the symptomology depends on the concentration of monoclonal Ig. The treatment is emergency plasmapheresis.
 - *Platelet dysfunction:* by thrombopathy (the binding of monoclonal Ig to platelets decreases their adhesion) treated by

corticoids or plasmapheresis; or thrombocytosis: rare in MM, but frequent 50 % in POEMS syndrome.

- *Monoclonal Ig autoantibody activity:* it is particularly the anti-polymerase circulating anticoagulants (which can induce a thrombotic risk but also a haemorrhagic risk by interfering with fibrin formation) and more rarely anti-factor circulating anticoagulants (anti-II and anti-VIII) or those with a heparin-like activity.
- *Acquired von Willebrand Syndrome (AvWS),* revealed by abnormal Willebrand laboratory tests, in the absence of a familial or personal history of the disease. These anomalies are corrected after anti-tumour treatment.

The AvWS is secondary to chronic lymphoproliferative syndrome in 50 % of cases (more often MGUS than a MM). The mechanism can result in an anti-Willebrand factor autoantibody activity of the monoclonal Ig, with absorption of VWF on the myelomatous cells, an increase in VWF degradation or a decrease in VWF synthesis. Usually, it is a type 2 Willebrand disease (qualitative: a more significant decrease in the VWF activity than the VWF antigen with a ratio of ≤ 0.7).

■ RFs due to anti-tumour treatment

The risk of major thrombopenia (grade 3: platelets between 10 and 50 G/l or grade 4: < 10 G/l) is raised while undergoing treatment by Bortezomib (Velcade®).

Thrombopenia arises in 30 % of cases (all grades: 43 %); it is cyclic: the platelets decrease from day 1 to day 11 (nadir), followed by an increase and normalisation from day 12 to day 21 (rest period). The aggregation tests show a decrease in the ADP response. Under treatment, monitoring of the platelet count is required before and during therapy: the therapy is not started if the platelet count is < 70 G/l and the treatment is stopped if the platelet count is < 30 G/l. A platelet transfusion may be necessary.

Bortezomib has however an anti-thrombotic effect by the bias of an increase of the endothelial TM and the efficacy of the response to protein C (increased coagulation inhibition).

Biological haemorrhagic markers

The haemostasis tests are often abnormal in a specific way for each anomaly:

- Bleeding time, prolonged closure time: thrombopenia, AVWS?
- Prolonged thrombin time (TT), prolonged reptilase time (RT): Anti-polymerase circulating anticoagulants
- Prolonged TT, RT normal: Heparin-like circulating anticoagulants?

Conclusion

The understanding of the thrombogenic mechanisms and myelomatous haemorrhagic mechanisms allow us to envisage the development of predictive markers and new therapeutic leads.

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