THROMBOSIS is a frequent and serious complication in patients with cancer. Caring for these patients can be clinically challenging, not least because it requires the coordinated efforts of a wide range of clinicians, highlighting the importance of a multidisciplinary approach. In her welcoming address, Dr Niamh O’Connell, Consultant Haematologist at the National Centre for Hereditary Coagulation Disorders, St James’s Hospital, Dublin, said this second Masterclass on Cancer and Thrombosis provided an excellent opportunity for medical oncologists, surgical oncologists, haematologists, palliative care physicians, researchers in the field of Cancer Associated Thrombosis and other colleagues in the multidisciplinary team to come together to ultimately benefit patient care.

“The purpose of this meeting is to work together to identify best practice, to improve quality of care, and to improve our standards. I hope that from this meeting, as with the previous Masterclass, we can make some progress in these areas,” she concluded.

Venous Thromboembolism in the Advanced Cancer Setting

Dr Simon Noble

Dr Simon Noble, a leading UK palliative care physician, highlighted the importance of listening to cancer patients at risk of venous thromboembolism (VTE) and involving them in decisions relating to thromboprophylaxis and treatment, as often patients' views are different than expected.

While evidence-based treatment is low-molecular-weight heparin (LMWH) by daily subcutaneous injection, he said the concerns of some doctors that these regular injections adversely affect patients' quality of life, particularly in those with advanced cancer, were unfounded, as the majority of patients rank efficacy and safety over convenience of administration when stating their preference for antithrombotic therapy.

Dr Noble, who is clinical reader in palliative medicine at the Institute of Cancer and Genetics, Cardiff University School of Medicine, said that increasingly cancer patients are living longer with metastatic disease, which further raises the risk of thrombosis and complicates its management. The optimal treatment and prevention of VTE in this patient group will continue to be clinically challenging, but it must be addressed, he stressed.

With scant evidence to guide the clinician in this particularly difficult situation, he advised doctors attending the Masterclass on Cancer and Thrombosis to go ‘old school’ and tailor management to the individual based on best available clinical evidence, an understanding of the pathophysiology of the condition and of pharmacology, and after full discussion with patients of the risks of each treatment option.

CAT clinic

An honorary consultant in palliative medicine at Royal Gwent Hospital, Dr Noble established a multidisciplinary Cancer-Associated Thrombosis (CAT) Clinic almost two years ago to tackle an increasing number of advanced cancer patients presenting with thrombosis, who he felt were not being managed optimally. This dedicated service has grown exponentially and sees 300 new patients a year.

“Cancer-associated thrombosis is a different beast, it’s not just that patients with cancer get more clots or they get them more readily, they actually form different clots, which are more challenging to treat,” he said.

He explained that a fractal analysis of the viscoelastic properties of incipient blood clots, which is constant at a fractal dimension of 1.74 in healthy volunteers, was different in lung cancer patients. The incipient clot is formed at the gel point of coagulating blood – the point where blood begins to change from liquid to ‘solid’. “The theory is that the baby clot forms a template for the big clot,” he noted.

“We looked at a large number of lung cancer patients and demonstrated that the fractal dimension is higher; the number isn’t much greater but when it’s an exponent, the clot formed has a density about four times that of healthy blood.” So, what we’re beginning to understand is that the...
clots that form with cancer are denser and sometimes they form more quickly.”

Treatment challenges

CAT is more difficult to treat than thrombosis in non-cancer patients, and confers a poorer prognosis, most likely because of a more aggressive cancer associated with a clot. He also remarked that a significant number of cancer patients experience treatment failure on warfarin, either failure to resolve the clot or recurrent thrombosis. In addition, there is an increase in bleeding even if INR levels are maintained within stable limits.

“In palliative care patients, it takes monitoring every other day to try to maintain a stable INR, and when you're having a blood test done every other day there are all sorts of inconveniences and uncertainties introduced. Warfarin is not the ideal drug. We know that LMWH is now the gold standard,” said Dr Noble.

He highlighted several studies, beginning with CLOT, which establish LMWH as the treatment of choice in CAT. The CLOT trial demonstrated a risk reduction of 52% – the probability of recurrent thromboembolism was 17% in the warfarin group and 9% in the LMWH group.

“If we look at all the studies that have been published, we’re beginning to see a pattern that LMWH is more efficacious than warfarin and also there is not a statistically significant increase in bleeding. As a result of this data, international guidelines all say very much the same thing, which is LMWH over warfarin for the treatment of cancer-associated thrombosis. Recommendations state six months, or three to six months, and if you have ongoing active cancer, to consider anticoagulation beyond that.”

CLOT results

Despite this, when the CLOT results were published in 2003, Dr Noble said he had some difficulty convincing colleagues to switch from the oral warfarin therapy to LMWH as the perception abroad was that the burden of daily injections would prove an unwarranted hardship on an already vulnerable patient group.

As a result he performed two qualitative studies to gauge the patient’s experience and preferences in this regard. Both his 2005 and 2014 studies confirmed that LMWH is not only an acceptable intervention; it conferred more freedom to the patient compared to warfarin treatment and was an acceptable trade-off against patients’ strongly negative experiences of symptomatic VTE.

“Patients found LMWH acceptable; none of them said they enjoyed it, or looked forward to it, but saw it as a necessary evil. What also happened is they developed rituals to do with the administration of it, and they normalised this unusual and abnormal experience,” Dr Noble said.

“However, a result that we had not anticipated was that many of the patients said they felt their experience of cancer-associated thrombosis was more distressing than their cancer diagnosis.”

PELICAN study

Following up on this finding, Dr Noble and colleagues conducted the PELICAN study, which explored the patient experience of living with CAT. The research results are in press.

“Cancer patients need support and education. Without it, the sudden onset of CAT, when all hell breaks loose, is quite traumatic for the patient. We've developed sepsis pathways we need to be developing pathways or systems by which we manage this equally injurious complication,” he said.

With regard to novel oral anticoagulants (NOACs), which have demonstrated non-inferiority to warfarin, Dr Noble reminded the Masterclass that warfarin is not as efficacious as LMWH, the current gold standard. His research has confirmed that, although most patients would prefer the oral route to the subcutaneous route, this would only be on the proviso of equal efficacy and safety.

He concluded that since NOACs have not demonstrated non-inferiority against LMWH, it would seem counterintuitive to recommend NOACs routinely as first-line treatment of CAT.

“That's why it's important to listen to the patient because they are very clear; they want efficacy and safety over convenience. Patients would say ‘I'm not asking you to give me the second best chemotherapy so I don't want you to give me the second best anticoagulant’.”

References

Important research conducted at Cork University Hospital (CUH) on thrombosis in myeloma patients was presented by lead author, Dr Maeve Crowley, a Haematology Specialist Registrar in the Cork Coagulation Centre, CUH and University College Cork.

She told the Masterclass on Cancer and Thrombosis that patients with myeloma demonstrated laboratory evidence of hypercoagulability when compared with healthy controls, which appeared to decrease on treatment. Thromboprophylaxis in myeloma patients also varied widely in Ireland.

A high rate of venous thromboembolism (VTE) has been reported in patients with myeloma since 1970.1 More recently, increased rates of VTE have been noted in myeloma patients on specific treatment regimens. “The IMiDs thalidomide and lenalidomide mainly have been suggested as the culprits,” she observed.

Monoclonal gammopathy of undetermined significance (MGUS) is considered a pre-malignant condition with increased risk of development of a B-cell neoplasm, and has about a 1% per-year rate of transformation to multiple myeloma. It has yet to be precisely determined what magnitude of VTE risk exists, if any, in the MGUS population.

**Retrospective review**

Dr Crowley and colleagues conducted a retrospective review of all myeloma patients attending CUH to investigate the rate of VTE and looked at the risk factors associated with it.2

Of 217 patients, 12% had an episode of VTE, 69% received at least one immunomodulatory agent, and 95% had low or intermediate risk of VTE according to the Khorana score (an assessment score commonly used to estimate the risk of VTE in cancer patients, but validated in solid organ tumours).

Although VTE was a frequent occurrence in this cohort and patients had many VTE risk factors (sex, myeloma subtype, ISS, presence of a second malignancy, IMiD exposure, number of regimens), no one factor was predictive. “We did not find the Khorana score predictive,” she added.

In another study, Dr Crowley and colleagues decided to investigate the differing coagulation profiles of patients with myeloma and MGUS by means of conventional coagulation tests and thromboelastography.3 Eight patients were recruited into each of three groups – myeloma, MGUS, healthy controls.

“This was the first study to show that patients with myeloma, MGUS and normal controls form three distinct groups in terms of laboratory coagulation parameters,” said Dr Crowley, noting that the coagulation profile of the MGUS patients was intermediate between the myeloma patients and the normal controls. There was no significant difference in thromboelastographic parameters between the three groups.

Using the same patient cohort, the CUH researchers performed Calibrated Automated Thrombography (an in-vitro assay of plasma thrombin generation) on platelet poor plasma and found that peak thrombin generation was significantly higher in myeloma and MGUS patients relative to healthy controls, and there was reduced sensitivity to anticoagulant activity of activated protein C (APC) in myeloma and MGUS patients relative to controls.

In a third study, an additional eight patients were recruited (16 myeloma patients in total) to look at the evolving haemostatic pattern in patients with myeloma on treatment.4

**Coagulation profiles**

“This study supports the hypothesis that the coagulation profiles of patients with myeloma are abnormal at baseline and change as they progress through cycles of chemotherapy. Their haemoglobin levels rose and their power protein levels fell as patients progressed through treatment cycles, indicating that patients were responding to the treatment, which suggests that as myeloma improves the coagulation profile also improves,” Dr Crowley said.

Finally, Dr Crowley detailed results of the first national survey of thromboprophylaxis use by haematologists caring for myeloma patients in Ireland, which she also spearheaded.5 Thromboprophylaxis practices were found to vary widely. Several thromboprophylactic agents, at varying doses, were used, as well as some use of novel oral anticoagulants (NOACs), which is not recommended in international guidelines.

There was no consensus on who should get thromboprophylaxis other than those on IMiDs in combination with chemotherapy/steroids or those who are high risk for VTE, aside from their myeloma. Disease burden was not considered by most when risk stratifying patients, which is contrary to other cancers where disease burden is considered important.

References
Prof James O’Donnell, Professor of Haematology in Trinity College and St James’s Hospital, Dublin, discussed the practical management of patients with cancer-associated thrombosis (CAT), in the context of delivering anticoagulation therapy to these challenging patients, during the second Masterclass on Cancer and Thrombosis.

Focusing initially on patients with haematological malignancies, Prof O’Donnell pointed out that recent data has clearly demonstrated a significant rate of thrombotic complications in cancers that affect the blood, bone marrow and lymph nodes.

He explained that the incidence of venous thromboembolism (VTE) is over 5% in patients with acute leukaemia,1 and in acute promyeloid leukaemia (APML), VTE rates climb up to 30%; the majority of these clots occurring in the first month of cancer diagnosis.2

Thrombosis is also prevalent in lymphoma patients, particularly in the non-Hodgkin’s lymphoma (NHL) group, in which there is an increased VTE risk for high grade NHL of 10.6% versus low grade NHL (5.8%), with an overall risk probably of 5-7%.3,4

“This means lymphoma patients have the third highest risk of VTE after upper GI cancer and lung cancer,” Prof O’Donnell noted.

In patients with Hodgkin’s disease, those who develop CNS lymphoma have VTE rates of approximately 60%,5 of which 7% will be fatal.2 Multiple myeloma also confers a significant thrombosis risk, with the cumulative risk of VTE increased nine-fold compared to matched controls.6

Increased risk

However, he stressed that the risk of venous thrombosis is increased five- to six-fold in all patients with underlying cancer, “such that about 20% of all cancer patients will develop a clinical venous thrombosis during the course of their illness”.

Prof O’Donnell highlighted two major issues that physicians face in treating and preventing VTE in cancer patients; the risk of developing both recurrent thrombotic events and bleeding complications is significantly increased in these patients during anticoagulant therapy.

Bearing those two factors in mind, he said the optimal treatment regimen for patients who develop cancer-related thrombosis, be it haematological or otherwise, is typically considered in two distinct parts: the initial management of these patients, which is the first five to seven days, and the ongoing treatment, which is three to six months.

Consensus guidelines on both the acute treatment and the long-term management of cancer-related VTE are quite similar. The American Society of Clinical Oncology (ASCO) suggests that low-molecular-weight heparin (LMWH) should be preferred over unfractionated heparin (UFH) for first five to 10 days; similarly the National Comprehensive Cancer Network (NCCN) guidelines recommend LMWH as initial treatment of choice.

Consensus guidelines (ASCO 2013; American College of Chest Physicians [ACCP] 2012; National Comprehensive Cancer Network [NCCN] 2011) also agree that LMWH is the treatment of choice for the long-term management of CAT.

Although guidelines are less specific in terms of optimal duration of anticoagulation therapy (ranging from three to six months and beyond), he said that at St James’s Hospital CAT is treated for six months.

Prof O’Donnell went on to recommend LMWH dose escalation as the preferred option for recurrent VTE in patients with cancer – either to 100% dose if recurrence occurs on 75%, or to 125% if previously on 100% dose.

He also stressed that incidental VTE in cancer patients “should be treated and should be treated with LMWH,” as per international guidelines.

“I think the evidence base that we have for the management of cancer-related VTE is pretty awful, so in terms of defining optimal management of these patients we desperately need large, adequately powered clinical trials to be performed,” he concluded.

References
Results from the CATCH trial – the largest study in cancer-associated thrombosis – have reinforced international guidelines supporting the use of low-molecular-weight heparin (LMWH) over warfarin for the prevention of recurrent blood clots in patients with active cancer.

Dr John Stinson, Senior Medical Advisor (Thrombosis) at LEO Pharma, who presented the results of this global study to Irish doctors during a Masterclass on Cancer and Thrombosis in St James’s Hospital recently, said treatment with tinzaparin cut the risk of venous thromboembolism (VTE) recurrence in cancer patients, while also reducing clinically relevant non-major bleeding, compared with warfarin.

Cause of death

He told the meeting that thrombosis is one of the leading causes of death in cancer patients. US MEDPAR Medicare Claims Data¹ revealed that the probability of death within 180 days of initial hospitalisation was more than three times higher among cancer patients with VTE compared to non-cancer patients with VTE (0.94 versus 0.29).

International consensus guidelines recommend the use of LMWH for the treatment of VTE for at least six months, as stated in the ASCO guidelines (2013),² the British Committee for Standards in Haematology (2011),³ and the European Society for Medical Oncology (2011);⁴ and for between three to six months, according to the American College of Chest Physicians guidelines (2012).⁵

Trial data

Results from a number of trials formed the basis of these recommendations, primarily the 2003 CLOT study, led by Prof Agnes Lee, in which the LMWH dalteparin was found to be superior to standard therapy warfarin.

The phase III CATCH study assessed the efficacy of the LMWH tinzaparin (innohep⁶) in preventing the recurrence of VTE in patients with active cancer who have had an acute VTE episode, compared to treatment with warfarin.⁶

Dr Stinson said this was a “truly global study” with 900 patients enrolled from 165 sites in 32 countries on five continents, including 44% enrolment from Asia and the Middle East.

A total of 449 patients were randomised to receive tinzaparin and 451 to warfarin. At the time of randomisation, 54.7% of the patients had metastatic disease and 52.9% had received anticancer treatment (chemotherapy, surgery, and/or radiation). Approximately 90% of patients completed the study protocol.

All patients started with tinzaparin 175 IU/kg for the first five to 10 days and then were either randomised to receive tinzaparin for a further six months or warfarin for six months.

Cancer sites

The most common sites of cancer were gynaecologic (203), lower GI (119), lung (104), haematological (94), and breast (84). A composite of symptomatic deep vein thrombosis (DVT), symptomatic pulmonary embolism (PE), fatal PE, incidental proximal DVT and incidental proximal PE served as the primary outcome measures. Major bleeding, clinically relevant non-major bleeding and overall mortality comprised the safety outcomes.

“In patients with active cancer and acute VTE, tinzaparin was found to reduce the cumulative risk of recurrent thrombosis from 10.5% [in the warfarin group] to 7.2% [HR 0.65; 0.41 to 1.03] and although that was not statistically significant, it was clinically significant,” said Dr Stinson.

“Tinzaparin significantly lowered the risk of symptomatic DVT by 52% (p=0.04) and did not increase major bleeding despite full dose. It also significantly reduced clinically relevant non-major bleeding (p=0.03).

“There was no difference in overall mortality between the two treatment arms,” he added.

References
5. Guyatt GH et al, Chest 2012; 141(2): 7S-47S.
Venous thromboembolism (VTE) occurs in approximately 10% of ovarian cancer patients - increasing to 11-27% in some histological subtypes such as clear cell cancer and adversely impacts on survival, said Dr Lucy Norris, a Senior Scientist at the Institute of Molecular Medicine’s Obstetrics and Gynaecology Laboratory Research Group in Trinity College Dublin (TCD).

She told the Masterclass on Cancer and Thrombosis that the management of VTE is challenging in gynaecological cancer patients, who often undergo major pelvic and abdominal surgery and receive combination chemotherapy, each of these treatments significantly increasing the risk of thrombosis.

Predicting which patients are most at risk is key, Dr Norris said. Her research group is uniquely positioned to investigate the pathogenesis of thrombosis in gynaecological cancer, and the potential to develop new risk models, by means of access to the TCD Gynaecology Cancer Bioresource, which has an extensive biobank of blood and tissue samples from more than 1,100 cancer patients, as well as the Gynaecological Cancer Centre in St James’s Hospital - one of the largest in the country with more than 300 cases per annum.

Guidelines

In 2012, international guidelines recommended extending low-molecular-weight heparin (LMWH) post-operative prophylaxis up to four weeks in patients undergoing major abdominal or pelvic surgery for cancer. Prior to this, standard measures for this patient group included:

- LMWH prophylaxis (4,500 units BMI <30) for duration of hospital stay
- Early mobilisation
- Hydration
- Compression stockings.

“Despite these standard measures, a significant number of patients develop VTE post surgery, often in the immediate post-surgery period,” said Dr Norris.

Audit

An audit of the VTE incidence in ovarian cancer patients at St James’s Hospital, prior to the extended prophylaxis guidelines, identified an overall incidence of 9.7% and found that one-third of thrombotic events occurred pre-operatively, one-third after surgery (28 days) and one-third were recorded late post operatively. VTE also adversely affected survival.

A second audit was undertaken to evaluate the effectiveness of extended post-operative prophylaxis in ovarian cancer patients by calculating the incidence of VTE in this population from January 2012 to December 2013. Although the incidence rate was similar (9.5%), the post-op VTE incidence in the first 28 days was substantially reduced.

Thromboprophylaxis

“Extended thromboprophylaxis does reduce VTE events post surgery but, in a lot of patients, we still see thrombosis despite heparin prophylaxis,” she noted.

The study highlighted the need for biomarkers to identify high-risk gynaecological cancer patients. Several biomarkers for thrombosis in cancer were found in the Vienna Cancer and Thrombosis Study (CATS) cohort, including D-dimer, P-Selectin, thrombin generation, and factor VIII activity. Combining biomarkers with the Khorana risk score further increased the cumulative probability of VTE from 17% in those patients with the highest levels to 34%.

Dr Norris’s research group investigated thrombin generation as a biomarker for VTE in ovarian cancer patients before surgery, and thrombin generation in the post-operative period, as well as the effect of adjuvant chemotherapy on thrombin generation.

“We concluded that thrombin generation tests have potential as biomarkers of VTE in gynaecological cancers. Patients who develop VTE in the post-operative period have evidence of hypercoagulability before the VTE event despite LMWH prophylaxis. Anti-Xa levels appear to be suboptimal in many of the patients post surgery and chemotherapy appears to increase thrombin generation in an APC [activated protein C] dependent manner,” she said.

The research group also looked at thromboelastography (TEG) as a tool for detecting hypercoagulability in gynaecological cancer patients undergoing surgery. They found that TEG analysis showed an increase in clot strength in patients with malignancy, therefore could have potential as a biomarker for hypercoagulability in gynaecological cancer patients.

Dr Norris also highlighted a new study launched last year, which aims to develop a risk model for the prediction of VTE in gynaecological cancer patients using a combination of clinical risk factors and biomarkers.

References
Low-molecular-weight heparins are a large and complex family of heterogeneous and multi-targeted agents, and the drug of choice in the “battle against the clot” in cancer patients, said Ismaïl Elalamy, Professor of Haematology and Head of the Department of Haematology at T enon University Hospital, Paris.

He described low-molecular-weight heparins (LMWHs) as a veritable “Swiss army knife model of a drug with multiple actions, multiple effect and multiple targets,” therefore a physician must carefully select which drug will maximise the benefit for a particular patient.

Just as thrombosis is a multi-dimensional process, he explained that there are four dimensions a doctor might consider when deciding on anti-thrombotic treatment with LMWHs: patient characteristics, the type of cancer, active treatment, and the fourth “biological” dimension – biomarkers of hypercoagulability and the biological properties of a LMWH.

Thrombosis

Thrombosis is a major complication of cancer, often leading to a poorer prognosis, and is also considered to be a harbinger of cancer, said Prof Elalamy. “LMWH is drug of choice regarding this battle against the clot in cancer patients,” he added.

“The hypercoagulable state of cancer is based on multicellular and very complex interactions,” he told the Masterclass on Cancer and Thrombosis, remarking that thrombosis in cancer relates principally to the procoagulant properties of tumour cells themselves, tumour-associated endothelial cells, and host inflammatory cells.

The expression of the cell surface receptor protein tissue factor (TF) by cancer cells, as well as the formation of procoagulant microparticles derived from the activation of platelets, are pivotal events leading to enhanced thrombin generation in patients with cancer.

“We know that tissue factor is a trigger of the coagulation cascade but it is also a cornerstone for other biological processes such as tumour development and inflammation, and now we know that TF, which is expressed constantly by the tumour cell, is also a big factor regarding tumour angiogenesis and metastasis.”

“Tissue factor triggers thrombin generation through the coagulation cascade,” he said. “Thrombin in this localised regulation cascade leads to platelet activation, fibrin generation and clot formation. This fibrin network acts as a storehouse for numerous thrombogenic factors, protecting them from degradation, and it also acts as a scaffold for neoangiogenesis and tumour development. This bush-like clot also protects tumour cells from the immune system and the natural killer cells.”

He went on to discuss the production of LMWHs – biologic products extracted from natural glycosaminoglycans (GAG) porcine mast cells. LMWHs are manufactured from unfractionated heparin (UFH) by controlled depolymerisation using chemical (nitrous acid or alkaline hydrolysis) or enzymatic (heparinase) methods.

Anticoagulants

“We know that they are very heterogeneous with different polysaccharide chains and different lengths. Only a part of these chains possess the pentasaccharide domain, which is crucial to allow the anti-thrombin binding and the anticoagulant effect of heparins, but only 30% of these chains have the pentasaccharide domain.

“This means that 70% are not anticoagulant but does this mean that 70% of the chains are useless? There is an increasing interest in the effects of this 70%, which have different pharmacological activities leading to different clinical impact, some positive, some negative,” he said.

In addition, depending on the GAG chains length and composition they interact with other components, as in, they exchange with natural GAG of the receiver endothelium, they bind to receiver molecules, and they bind to receiver cells.

Underscoring the heterogeneity of LMWHs, Prof Elalamy said that LMWHs vary considerably with regard to their molecular weight, their Anti-Xa/Anti-IIa ratio, and their Anti-Xa activity based on a gravimetric approach.

He also noted that although UFH is cleared through the reticulo-endothelial system, LMWH is dependent on renal clearance; as a result, patients with renal failure are potentially at risk of bleeding because of reduced clearance and prolonged anticoagulant effects of LMWH.

Bleeding risk

He highlighted a study of 1,684 patients with VTE and cancer who were followed for 180 days after VTE diagnosis. Patients were treated mainly with LMWH or vitamin-K antagonists (VKA). The risk of major bleeding was increased in chronic kidney disease (CKD) patients with VTE and cancer, and was most prominent in those treated with LMWH and an eGFR < 30 mL min⁻¹, suggesting the LMWHs should be used with caution in this patient group.

However, he said there is also an increased risk of bleeding in patients with renal impairment who are prescribed a
VKA. Limdi et al found that patients with reduced kidney function required lower dosages of warfarin, had poorer control of anticoagulation and were at a higher risk for major haemorrhage.2

Indeed, Brodsky et al reported that warfarin-related nephropathy occurred in patients with and without chronic kidney disease and is associated with an increase in mortality.3

**Renal issues**

With regard to LMWHs in elderly patients, a 2002 French study investigated the safety profile of tinzaparin administered once daily at a standard curative dose in 200 very elderly patients.4 One-quarter of the study population had severe renal impairment. Prof Elalamy said there was no accumulation in one month of treatment in this patient population and only one fatal bleeding episode due to co-morbidities.

In a prospective North American study looking at enoxaparin use in patients with normal renal function compared to patient with moderate renal impairment, there was a significant increase of major bleeding in this second group.5

Prof Elalamy discussed the use of thrombin generation assay to detect and identify patients at-risk of thrombosis. Depending on the cancer cell line tested, certain cancers demonstrate a greater propensity to trigger thrombin generation in plasma, for example thrombin generation is highest in pancreas cancer, compared to breast.6

Regarding the effect of LMWHs in the inhibition of thrombin generation triggered by pancreatic cancer cell line in human plasma, he said Galea et al found that tinzaparin was more successful, compared to enoxaparin or nadroparin.7 “You need much less tinzaparin to inhibit 50% of thrombin generation, triggered by pancreatic cancer cell line in human plasma.” See figure for trial results.

**Tissue factor pathway**

He pointed out that tissue factor pathway inhibitor (TFPI), one of the most important inhibitors of blood coagulation, is released from the endothelial wall when LMWH is injected, effectively blocking the procoagulant (thrombosis), as well as the non-coagulant (inflammation, angiogenesis) effects mediated by tissue factor.

“It has been shown that LMWHs are able to inhibit angiogenesis using different models (chick embryo aortic ring model8 and HUVEC: human umbilical vein endothelial cells HUVEC model9),” he added.

Another study demonstrated variable in vitro selectin-blocking activities of LMWHs, with tinzaparin demonstrating the highest potency.10

“LMWHs are able to inhibit angiogenesis through TFPI release, to reduce thrombin generation, and to reduce the inflammatory response and the cell-to-cell interaction through P-selectins and L-selectins bridges. They are able also to reduce in animal models the metastatic spread and the proliferation of tumours due to heparanase inhibition, and last but not least, reduce this bush-like clot and facilitate the effect of natural killer cells, also minimising the resistance to chemotherapy of tumour cells protected by these bodyguard clots,”11 he told the Masterclass.

In his analogy of LMWH and diamonds with many facets, he urged doctors to “face the many faces” and investigate which agent is the right one for their cancer patient in order to prevent thrombosis and optimise prognosis.

**References**

Masterclass on Cancer & Thrombosis