Interview

Dr Anna Falanga speaks to Charlotte Barker, Commissioning Editor

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Anna Falanga is Director of the Hemostasis and Thrombosis Centre, Department of Hematology, Ospedali Riuniti in Bergamo, Italy and Professor at the School of Hematology, University of Milan, Bicocca, Italy. Having received her medical degree and board certification in internal medicine at the University of Naples, Italy, Dr Falanga obtained her board certification in hematology at the University of Verona, Italy. Subsequently, she spent 3 years working as a postdoctoral fellow in the Mario Negri Institute in Milan, Italy, and a further 2 years at the University of Colorado School of Medicine, Denver, CO, USA. Dr Falanga's research interests include the study of the interactions of malignant cells with the hemostatic system, the role of antithrombotic agents in human cancer and experimental models, and the management of venous thromboembolism in cancer patients. Dr Falanga became an elected member of the Scientific and Standardization Committee's Class 2008 in 2002, and Chairperson of the Sub-committee on Hemostasis and Malignancy from 2002 to 2006. She has an active role in many professional societies, including the American Society of Hematology and the American Society for Cancer Research. Dr Falanga is also a member of the committee on Hemostasis of the American Society of Hematology, and is the national coordinator of the Italian section of the Medical Women International Association.

How did you first become involved in research into thrombosis and cancer?

I have been involved in thrombosis research since I was a student. I prepared my final thesis for my degree in medicine (at the University of Naples, Italy) on the topic of atherosclerosis. Specifically, I was working on lipoproteins and arterial thrombosis. I then undertook a postdoctoral research fellowship at the Mario Negri Institute, Milan, in Dr Maria Benedetta Donati's group, working mainly on platelets, prostoglandins and their involvement in the thrombotic process. So I am an MD, but I started with a strong background in basic research.

There was some very interesting work being carried out in this field during the 1980s, and the Donati laboratory (along with Nicola Semeraro) was very involved with this. The starting point was the study of tumor cells and the realization that tumor cells could activate blood coagulation by themselves. At that time, information regarding the relationship between cancer and thrombosis was pretty clear. Studies had been carried out, for example, in 1981 by Dr Leo R Zacharski [1], in which the effect of warfarin anticoagulation on cancer survival was tested. In this study, warfarin was administered together with chemotherapy in cancer patients without thrombosis, which at that time was something really new. However, while interest in the biology of cancer and the properties that could link cancer to thrombosis was pretty strong, at that time there was more activity in the laboratory rather than in the clinic. The attention was mostly on the procoagulant activity of the tumor cells, the interaction of cancer cells with platelets and the endothelium, and the expression of tissue factor procoagulant activity by monocytes in patients with cancer, which was a demonstration that normal monocytic cells circulating in the blood of cancer patients could express, upon stimulation, more tissue factor than the same cells from normal controls. This influenced me to become involved in research specifically looking at the link between thrombosis and cancer.

While working at the Institute, there was the opportunity to take a fellowship in the USA, focusing on tumor cell procoagulant activity. I therefore spent 2 years in the USA and carried out research at the University of Colorado (CO, USA) with Dr Stuart Gordon, another person who influenced me a great deal.

Can you tell us a little about the research projects you are currently working on?

We have two main lines of research. One involves basic biological studies *in vitro* involving tumor cell lines of different origin. We are characterizing the prothrombotic properties of cells from different cell lines, such as leukemia, pancreatic cancer and prostate cancer cells. Not only are we studying the capacity of these cells to activate blood coagulation, but we are also using specific tests to characterize the other kinds of procoagulant properties they are expressing. For example, if the cells are expressing adhesive molecules, which indicate the capacity of these cells to adhere to the vascular endothelium, we can investigate this further using an experimental system of endothelial cells grown *in vitro*. We also have an experimental system testing the capacity of the medium of cancer cells grown *in vitro* to induce angiogenesis in the Matrigel model. In addition, we test the interference of drugs such as heparins and low-molecular-weight heparins (LMWHs) to interfere with these activities.

Our second line of research is to study the hypercoagulable state of patients with different types of cancer. This involves leukemic patients, multiple myeloma patients and, at present, we are studying gastrointestinal cancer patients and evaluating the level of interference of antitumor drugs with the hypercoagulable state. We hope to understand whether there are laboratory tests that can predict thrombosis in patients undergoing chemotherapy before therapy is initiated, to understand whether they can be selected for prophylaxis. We are also

trying to understand whether, when cancer patients receive particular therapies with proangiogenic or antiangiogenic (mainly antiangiogenic) properties, there is variation in these thrombotic markers and whether there is a downregulation of this hypercoagulable state in patients who are, for various reasons, receiving anticoagulant treatment.

Our group also participates in clinical trials of thrombosis with the new anticoagulants, but that involves mainly noncancer patients.

Why are cancer patients more prone to thromboembolism?

There are some general factors that influence the trend to thrombosis in these patients, which can be similar in other situations, for example, inflammation, sepsis, bed rest, previous history of thrombosis, necrosis and vascular stasis (sometimes there is a tumor mass that reduces the volume of the vessel walls and can induce a prothrombotic situation).

However, in addition, there are many other properties that are promoted by tumor cells and probably have an effect on the risk of tumor-associated thrombotic events. The capacity of tumor cells to produce their own procoagulant and fibrinolytic activities is important, as is the capacity of the cells to adhere to normal cells such as platelets, leukocytes and endothelial cells and hence activate their procoagulant activity, triggered by cell–cell contact with the tumor cells. In addition, tumor cells produce a number of inflammatory cytokines including IL1-β and TNF-α, and proangiogenic factors such as VEGF. The cytokines are known to induce the expression of tissue factor by endothelial cells and leukocytes, so all of these proteins produced by tumor cells can activate and induce the procoagulant features of normal cells. Normally, these cells do not produce procoagulant activity, but under inflammatory stimulation, they do.

Several papers are being published at present describing an increase in circulating microparticles in cancer versus noncancer patients, which probably come from the tumor cells and carry tissue factor in the circulation. This supports the hypothesis that one of the most important things could be the tumor *per se*, rather than the general factors.

So not only are there general factors that can be similar in other situations, there are also unique factors that characterize the pathogenesis of thrombosis in cancer.

Recent research suggests that cancer patients receiving heparins gain a survival advantage independent of thromboembolytic prophylaxis. Do these drugs have a direct antitumour effect? What mechanisms of action are thought to be involved?

It is possible that these drugs may have an anticancer effect. In general, we can assume that reducing the hypercoagulable state of cancer patients has a beneficial effect. The hypercoagulable markers increase with disease stage, so they are much more abnormal in advanced cancer patients compared with early-stage cancer patients. Also, there have been studies showing that there is a relationship between the levels of prothrombotic markers and the prognosis and survival of the patient. The first trial testing anticoagulation as adjuvant therapy in lung cancer was published as early as 1981 [1], so in a way the hypothesis that a reduction of blood coagulation or hemostatic proteins can have a beneficial effect in cancer patients is an old one.

A recent study, in which cancer patients without thrombosis were given the LMWH nadroparin along with chemotherapy, and compared with control patients given placebo and chemotherapy, demonstrated a small but significant increase in survival in patients receiving nadroparin, similar to that seen with much more expensive anticancer drugs [2].

A meta-analysis of studies testing LMWH for cancer survival, has also been published (by Nicole Kuderer in *Cancer*) [3]. From this analysis of 11 studies, it seems that LMWHs may have a better effect on survival than other anticoagulants and, theoretically, they may have anticoagulation-independent activity.

To understand the potential mechanisms of heparins, you must consider that proteins like thrombin, fibrin and tissue factor all have direct effects on tumor growth and dissemination besides their properties in clotting activation. So, inhibition of several patterns of clotting activation can inhibit other properties linked to the hemostatic proteins.

One potentially different mechanism involves the fact that heparins in general and LMWHs in particular may have an antiangiogenic capacity. We recently published a study in *Thrombosis Research* [4] demonstrating that different types of LMWHs reduced the angiogenesis induced by the medium of tumor cells *in vitro* in the Matrigel assay.

Heparins also inhibit a number of growth factors that are linked to the subendothelium through glycoaminoglycans, and once they become free in the environment, they are more active and induce tumor growth.

Another important effect is the inhibition of heparanase, an enzyme expressed at high levels in highly metastatic cells, which has activity not only in degrading the subendothelial matrix, but also helps growth factors to be liberated from the glycosaminoglycans of the cell surface membrane, thus increasing the potential to induce tumor growth and dissemination.

In addition, heparins induce inhibition of fibrin formation. This is important because fibrin has been demonstrated to form a coat around the tumor cells, and therefore acts as a shield that hides the cells, which cannot then be recognized by the NK system.

In conclusion, an anticoagulation-independent effect is a possibility, although there is no direct evidence as yet.

Do you think anticoagulants might become part of standard cancer therapy in the future?

The Kuderer meta-analysis suggested that this is a possibility, but more studies must be conducted. We cannot recommend that patients with cancer in general should receive LMWHs for increasing survival at this time, but the recommendation made in the American Society of Clinical Oncology (ASCO) guideline is that we should encourage patients to participate in trials testing this hypothesis.

Several groups have argued that prophylactic treatment for venous thromboembolism is underutilized in at-risk patients, including cancer patients. Would you agree with this? What do you think are the main barriers to effective prophylactic therapy in this population?

Yes, prophylactic treatment is underutilized. The first barrier is that there is a time lag between publication of guidelines and adoption by clinicians. Therefore, diffusion of the guidelines should be encouraged.

There is still a lot of room for further research, both at the basic and also the clinical level. There are limitations due to the lack of data in several areas. For instance, we can recommend prophylaxis in cancer patients who are hospitalized because they are considered at high risk, but none of the studies has been specifically conducted in cancer patients. In the setting of ambulatory cancer patients receiving either adjuvant or curative chemotherapy for metastatic disease there is a major lack of information. In addition, there is not a general agreement, based on the data available, on prolonged prophylaxis after surgery, except for those patients at very high risk. The Italian guidelines recommend this, but it depends on the panel as there are not many studies that can give a clear-cut indication.

Another problem that needs more study is bleeding in these patients, because the fear of bleeding can restrain clinicians from utilizing anticoagulant drugs.

You have been involved in preparing the recent ASCO guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. Why do you think there was a need for this guideline?

Firstly, the guideline was needed because there are new things that were not covered in previous guidelines and, secondly, because it is important that big institutions of oncologists start to get involved in this field, as this can very much raise the alert in terms of diagnosis and in understanding the magnitude of the problem.

Where do you think your research will be focused over the next 5 years?

We will continue our work in the basic research laboratory, and will also focus on studies of thrombotic markers in patients that are enrolled and followed-up prospectively to detect the occurrence of thrombosis. We hope to find out whether we can identify blood tests that can predict high-risk patients.

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