

Against clotting and cancer

Drs Marc Carrier and Rebecca Auer are hoping to reduce the postoperative occurrence of cancer metastasis by taking advantage of the anti-cancer and anti-coagulant properties of low molecular weight heparin



Can you explain the underlying mechanisms for the anti-coagulant and anti-cancer properties of low molecular weight heparin (LMWH)?

The anti-coagulant effect of heparins, including LMWH, is attributed to their ability to bind anti-thrombin and potentiate its inhibitory effect on the thrombin-activated factor Xa complex. This complex converts fibrinogen to fibrin, the final step in the formation of fibrin clots. LMWHs also have a number of other properties that are responsible for both their anti-coagulant and anti-metastatic properties. These include the ability to stimulate the production of tissue factor pathway inhibitor (TFPI), and inhibit platelet activation and aggregation by blocking P-selectin – a molecule on the surface of the platelets. These properties can prevent, in part, the formation of platelet and fibrin clots around tumour cell emboli thus facilitating natural killer cell clearance of the cancer cells and attenuating the formation of metastatic disease, particularly in the postoperative period. LMWHs also have some additional anti-cancer properties, including inhibiting tissue factor (TF)-mediated tumour invasion and blocking neovascularisation by preventing platelets from releasing growth factors – such as vascular endothelial growth

factor (VEGF) – or directly binding to and blocking the VEGF receptor.

How were these actions of LMWHs first identified?

The association between cancer and thrombosis was first identified by Armand Trousseau in 1865. Since that time, there have been countless pre-clinical studies exploring the effects of coagulation and various anti-coagulants, including LMWHs, on cancer metastases. In the 1990s, a number of clinical trials comparing unfractionated heparin and LMWH in cancer patients with deep vein thrombosis (DVT) suggested that LMWH was associated with a reduction in mortality that appeared to be related to improved cancer survival. This led to the conduct of four clinical trials that evaluated the ability of LMWH to improve survival in cancer patients without a DVT or pulmonary embolism (PE). The results, summarised in a meta-analysis, demonstrated that LMWH was associated with a 40 per cent reduction in death at two years. While this is an impressive result, the fact that the patients enrolled in these trials had a variety of different types and stages of cancer means that there is still insufficient evidence to recommend the use of LMWH as a cancer therapy.

What is the basis of the thromboprophylactic effect of tinzaparin, the drug at the centre of this clinical trial? Are you aware of any limitations to the effectiveness of the drug?

Tinzaparin, like all LMWHs, binds to anti-thrombin, inhibiting coagulation by preventing the conversion of fibrinogen to fibrin. The efficacy of tinzaparin in averting

postoperative DVT and PE was established following publication of randomised clinical trials in the 1990s. The major limitation in the perioperative setting is obvious – haemorrhage. Major bleeding, defined as bleeding requiring a transfusion of more than 2 units of blood, occurs in less than 3 per cent of patients and only very rarely is reoperation required.

Do you have any preliminary results from the trial that you would like to discuss?

We performed a pilot study to ensure feasibility of the clinical trial. The results were peer-reviewed and published in 2011 in *Blood Coagulation & Fibrinolysis*. From this study we learned that, while some patients were reluctant to have an injection once a day for an unknown benefit, those patients who enrolled in the study had excellent compliance with very few missed doses of tinzaparin. Moreover, there were no serious bleeding complications following surgery.

Has a multidisciplinary approach proved important to the success of the project?

This project is an excellent example of translational and multidisciplinary research. The initial ideas and hypotheses were generated from animal models in Auer's lab. Collaboration with Carrier's clinical research unit allowed the building of the clinical trial infrastructure and facilitated the necessary assessment to determine if these exciting preclinical results were applicable to human subjects. The success of the trial depends on close collaboration between colorectal cancer surgeons, haematologists (anti-coagulant experts), anaesthesiologist and nurses.

Perioperative **metastasis**

A new clinical trial, from the **Ottawa Hospital Research Institute** in Canada, hopes to show that lengthening administration duration of a common post-surgical drug can confer anti-metastatic benefits in cancer patients

THE EXPERIENCE OF undergoing major surgery exposes the human body to significant physiological stress. One of the consequences of this is a disruption and over stimulation of the natural blood clotting cascade, the response of which is exaggerated postoperatively. Consequently, patients are susceptible to complications as a result of hypercoagulability – an abnormality of blood coagulation – that increases the risk of thrombosis (blood clots in vessels) in the forms of deep vein thrombosis (DVT) or pulmonary embolism (PE, blockage of the main blood vessel in the lungs).

Experimental research to determine the mechanisms underlying this effect has demonstrated that postoperative hypercoagulability arises in two ways. Firstly, surgical tissue trauma stimulates the release

of a protein called 'tissue factor' that initiates the coagulation cascade, ultimately resulting in the excessive formation of fibrin, the fibrous constituent of blood clots. Occurring alongside this process, platelets – cell fragments that release growth factors and contribute to blood clotting – become activated and aggregate, creating 'platelet plugs' around which the fibrin-based blood clots can form.

Studies carried out by Drs Marc Carrier and Rebecca Auer, from the Ottawa Hospital Research Institute, are investigating the links between the mechanisms involved in hypercoagulability and the metastasis of cancer. Auer's laboratory has shown that the mechanisms underlying postoperative hypercoagulability are responsible for enhancing the formation of metastases. This is thought to occur because blood clots form around tumour cells,

offering them protection from the innate immune system's natural killer cells. "Natural killer cells are extremely important in the clearance of cancer. Inhibition of their activity following surgery makes the postoperative period a uniquely susceptible time for the establishment of cancer metastases," explains Auer.

ANTI-COAGULANT THERAPY

To prevent the development of damaging and potentially fatal thrombosis, the hypercoagulability of surgical patients is routinely treated with anti-coagulant drugs based upon herapins – particularly low molecular weight herapins (LMWHs) – whilst they are hospitalised following surgery. Studies investigating postoperative hypercoagulability show that this state lasts for at least four weeks following surgery. Currently, however, the period of hospitalisation for patients undergoing, for example, colon cancer resection (the patient population involved in the present study), is only three to five days, after which time the administration of anti-coagulants is stopped.

In cancer patients, since it is also known that LMWHs confer anti-metastatic benefits, Carrier and Auer hypothesised: "It is critical to continue LMWH for the entire duration of postoperative hypercoagulability, at least four weeks after surgery, and very likely longer". In order to test this theory, the researchers are carrying out a clinical trial to study the effects of extending anti-coagulant treatment from before surgical resection, right through to the immediate perioperative period and for a total of eight weeks postoperatively. This would ensure that the hypercoagulable and highly susceptible period is covered, protecting the cancer patient from metastases until chemotherapy treatment was started.

PERIOP-01

Carrier and Auer's trial, entitled 'A multicentre randomised controlled trial of the use of extended perioperative LMWH to improve cancer specific survival following surgical resection of colon cancer' (PERIOP-01), aims to assess whether the extended use of anti-coagulant therapy following colon cancer resection increases 'disease-free survival' in subjects. The LMWH-based prophylactic drug being used in this trial is tinzaparin. In addition to extending the postoperative duration of prophylactic treatment of hypercoagulability, therapy was started as soon as the decision had been made to proceed with a clinical resection, instead of waiting until after surgery. "The rationale to initiate LMWH as early as possible was that metastases may be forming at any time prior to surgery. Whilst many researchers would advocate for starting LMWH at the time of diagnosis, this would not be a feasible clinical trial design," elaborates Carrier.



The clinical trial, in addition to assessing the potential of tinzaparin to reduce metastasis, aims to assess the safety of extended perioperative LMWH use. Because of its anti-coagulant nature, LMWHs can cause haemorrhage by reducing the normal clotting process that is vital following surgery to repair the internal damage caused by the treatment. It needs to be established whether there is an increased risk when use is extended to eight weeks, beyond the short period of hospitalisation.

ENHANCING UNDERSTANDING

The clinical trial aims to recruit 1,075 subjects over a period of four years. With such a large number of participants there is great potential for the research to significantly contribute to the currently limited understanding of how surgical procedures can encourage cancer metastasis. This is a serious problem in health services. Cancer surgery is an essential part of a curative cancer treatment plan for all patients with solid tumours. Despite this, many patients still die of their cancer as a result of metastatic disease. It is therefore a clinical priority to improve understanding of the pathological mechanisms underlying metastasis following surgery.

The ability to closely study the mechanisms by which LMWH confers anti-metastatic effects in surgical cancer patients, and comparing their recovery with that of the control subjects, will help to increase understanding of the physiological mechanisms involved in metastasis. This will be achieved through correlative assays performed on blood and tumour samples collected from patients at various time points before, during and after surgery. Additionally, follow-up monitoring – involving analysis of carcinoembryonic antigen (cancer marker) levels, annual CT scans of the abdomen and pelvis, chest X-rays and colonoscopies – will be continued for three years.

THE STATE OF PLAY

The PERIOP-01 trial has been fully developed and approved for accepting subjects with recently diagnosed colon cancer, who are to be treated with surgical resection. The researchers

THE PERIOP-01 TRIAL STUDY POPULATION

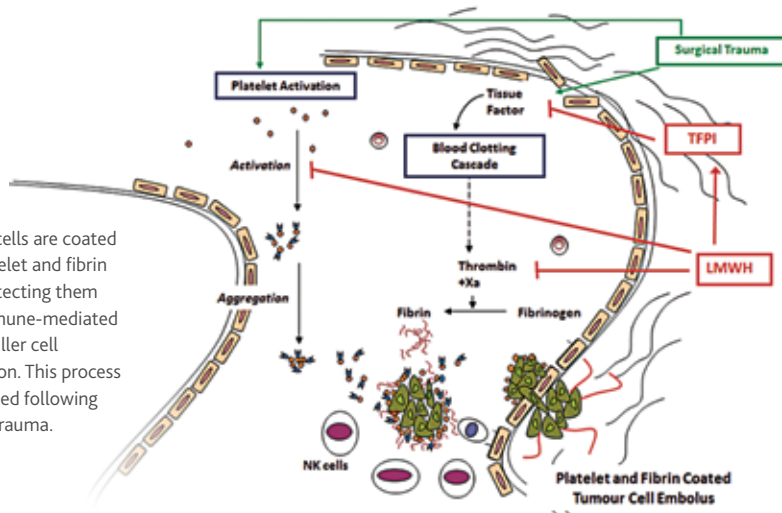
1,075 males and females meeting the following eligibility criteria are being recruited over four years:

- Pathologically-confirmed invasive adenocarcinoma of the colon
- Preoperative work-up that reveals potential resectability
- Preoperative work-up that reveals no evidence of metastatic disease
- A planned resection of the colon cancer within six weeks from the date of randomisation
- Age ≥ 18 years
- Haemoglobin ≥ 80 g/L

are currently in the early stages of recruitment focusing on five medical centres – one in Montreal, two in Ottawa and two in Toronto.

Looking forward, the trial aims to expand to incorporate centres across Canada and internationally to ensure sufficient patients are enrolled. This process should begin by mid-2014, and enrolment will continue throughout the following four years, to be completed by 2018. Certainly, by including more sites in the trial the size of the subject pool will be maximised, increasing the validity and significance of the results. The trial is an extensive undertaking, with Carrier foreseeing that: "The data will be fully analysed, after the five-year follow-up of the last recruited patients, in 2023". Although this seems a long way off, preliminary results and data will be collected and investigated at regular intervals throughout the process, with interim analyses planned for 2016 and 2020. These results will be able to guide the remainder of the trial and provide insight into the potential benefits that implementation of this therapeutic approach to perioperative care will confer, not only for cancer patients, but for all individuals undergoing surgery.

Tumour cells are coated with platelet and fibrin clots protecting them from immune-mediated natural killer cell destruction. This process is enhanced following surgical trauma.



INTELLIGENCE

PERIOP-01

OBJECTIVES

The primary objective is to assess the efficacy of extended perioperative thromboprophylaxis using tinzaparin to increase disease-free survival in subjects with resectable colon cancer. Alongside this, the study will assess the safety of extended perioperative thromboprophylaxis and evaluate the pro-metastatic mechanisms of surgery and the anti-metastatic mechanisms of low molecular weight heparin.

KEY COLLABORATORS

Canada: **Dr Tim Asmis**; **Dr Derek Jonker**; **Dr Gregoire LeGal**, The Ottawa Hospital, Ottawa • **Dr Paul Karanicolas**, Sunnybrook Health Sciences Centre, Toronto • **Dr Peter Stotland**, North York General Hospital, Toronto • **Dr Vicky Tagalakis**, Jewish General Hospital, Montreal • **Dr Joel Weaver**, Queensway Carleton Hospital, Ottawa

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CONTACT

Dr Marc Carrier and **Dr Rebecca Auer**

Divisions of Hematology and Clinical Epidemiology Program
Ottawa Hospital Research Institute
General Campus
501 Smyth Road Bin 180
Ottawa, Ontario K1H 8L6
Canada

T +1 613 737 8899 x 71393
E mcarrier@ottawahospital.on.ca
E rauer@ottawahospital.on.ca

www.ohri.ca

MARC CARRIER, MD MSc FRCPC is

Associate Professor in the Faculty of Medicine and Scientist in the Clinical Epidemiology Program of the Ottawa Hospital Research Institute. He holds a Tier 2 Research Chair in Venous Thromboembolism and Cancer from the University of Ottawa and a New Investigator Award from the Heart and Stroke Foundation of Canada.

REBECCA AUER, PhD is a surgical

oncologist specialising in colorectal cancer and abdominal sarcomas at The Ottawa Hospital, General Campus. She is Assistant Professor in the Department of Surgery at the University of Ottawa and Scientist in the Center for Cancer Therapeutics at the Ottawa Hospital Research Institute. She holds a New Investigator Award from the Canadian Institutes of Health Research.



Ottawa Hospital
Research Institute
Institut de recherche
de l'Hôpital d'Ottawa