

## Letters to the Editor

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### The use of extended perioperative low molecular weight heparin (tinzaparin) to improve disease-free survival following surgical resection of colon cancer: a pilot randomized controlled trial

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There is a well established link between hypercoagulability and cancer prognosis. Several studies have demonstrated that patients who experience a venous thromboembolic event (VTE) within a year of their cancer diagnosis have more advanced tumors and a worse overall prognosis [1] and that patients who develop a VTE during chemotherapy tend to die earlier [2,3].

A recently published meta-analysis showed that the use of prophylactic low molecular weight heparin (LMWH), in addition to standard therapy, was associated with an improvement in survival in patients with solid malignancies with a 40% reduction in the odds of death at 2 years [4]. The reduction in mortality was not the result of differences in fatal VTE or fatal bleeding events. Although the review supports a concept that LMWH possesses an anticancer activity, the differences in tumor type, stage and overall prognosis for the patients included within these studies make it difficult to establish definitive recommendations regarding the use of LMWH in cancer patients with no history of VTE [5].

The metastatic cascade is a complex and highly regulated series of events that involves interplay between hemostatic and angiogenesis-related processes [6,7]. Surgery appears to promote a pro-metastatic state. Surgical stress alone can augment tumor metastases in several animal models and the number of metastatic deposits that develop is directly proportional to the magnitude of surgical stress experienced by the animal [8,9]. There are a number of proposed mechanisms for the pro-metastatic effect of surgery: dissemination of tumor cells into the circulation [10,11]; protection of tumor cells in the circulation through stimulation of systemic

coagulation and platelet aggregation; and enhanced neovascularization of micrometastases by enhancement of angiogenesis [12]. LMWH appears to exert anticancer effect by inhibiting various steps in the metastatic cascade: suppressing tumor cell invasion of the extracellular matrix through tissue factor inhibition; hindering protection of tumor cells in the circulation from natural killer cell destruction via their anticoagulant and anti-platelet properties; and impairing neovascularization of micrometastases due to an antiangiogenic effect [7]. Hence, the perioperative period may be the optimal time to influence the development of metastatic disease using LMWH. We sought to assess the feasibility of an open randomized controlled trial (RCT) assessing the effect of extended perioperative LMWH thromboprophylaxis (tinzaparin) on disease-free survival in patients with resectable colon cancer.

Consecutive patients diagnosed with localized and resectable colon cancer assessed at The Ottawa Hospital were approached to participate into the study (July 2009–June 2010). Localized and resectable colon cancer was defined as: adenocarcinoma of the colon; preoperative work-up that reveals potential resectability [computed tomography (CT) scan or magnetic resonance imaging (MRI) of the abdomen within 8 weeks of enrolment]; and preoperative work-up that reveals no evidence of metastatic disease (CT scan or MRI of the abdomen and chest X-ray or CT scan of the chest within 8 weeks of enrolment). Patients were excluded if they had rectal adenocarcinoma (defined as tumor below the peritoneal reflection on imaging or within 12 cm of the anal verge by rigid sigmoidoscopy); prior VTE including deep vein thrombosis (DVT) or pulmonary embolism; requirement for full-dose perioperative anticoagulation; or contraindication to heparin therapy.

After obtaining written informed consent, patients were randomized to extended perioperative (intervention) or standard perioperative (control) thromboprophylaxis. Randomization was performed in permuted in blocks of two and four by the trial's statistician. Intervention allocation was determined by central randomization using sealed opaque envelopes. Patients randomized to extended perioperative thromboprophylaxis received a subcutaneous (s.c.) injection of tinzaparin (4500 U) daily beginning within 2 days of signing the surgical consent (up to 6 weeks before surgical resection) and continued for 4 weeks (up to day 28) following resection. The patients randomized to standard thromboprophylaxis only received s.c. tinzaparin 4500 U for the duration of hospitalization and the thromboprophylaxis was discontinued on the day of discharge. The first postoperative

dose of LMWH was administered 8 h following the completion of surgery, and all subsequent doses were administered daily in the evening. The study protocol was approved by our institutional review board.

The primary outcome measure was the recruitment rate. The secondary outcome measures included compliance with tinzaparin injections (i.e. missed doses), the rate of major and minor bleeding episodes while on thromboprophylaxis and disease recurrence. Disease recurrence was defined as local or distant (i.e. metastatic) disease recurrence or new primary colon cancer malignancy. Major bleeding episodes was defined as fatal bleeding; and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; and/or bleeding causing a fall in hemoglobin level of 20 g/l (1.24 mmol/l) or more, or leading to transfusion of two or more units of whole blood or red cells [13]. Minor bleeding events during follow-up defined as any bleeding not meeting the requirements of a major bleeding event.

Forty-one patients were approached between July 2009 and June 2010. Nine patients were ineligible, 23 refused consent and 18 patients (44%) were included. The recruitment rate was 1.6 patients per month (range 0–3). Ten of the included patients (56%) were men. The median age was 66 years. Resection was done by laparoscopy and laparotomy in 14 (77%) and 4 (23%) patients, respectively. Seven (39%) patients had stage II and six (33%) had stage III colon cancer. The median number of preoperative daily tinzaparin injections in patients randomized to extended perioperative thromboprophylaxis was 21 daily injections (range five to 33 injections). The median follow-up time was 9 months (range 4–17). No patient was lost to follow-up.

A total of two patients (11%) developed disease recurrence during a median follow-up of 13 months (range 6–18 months). One patient randomized to standard thromboprophylaxis developed liver metastases 10 months following the index cancer resection. Another patient randomized to extended perioperative thromboprophylaxis was diagnosed with an adrenal metastasis intraoperatively.

Tinzaparin thromboprophylaxis was well tolerated in all patients. No DVT or pulmonary embolism has been reported to date. Two (11%) major bleeding episodes were reported: a decrease in hemoglobin of 20 g/l that did not require transfusion (extended perioperative thromboprophylaxis group); a postoperative transfusion of two units (standard thromboprophylaxis group). No minor bleeding was reported.

Patient compliance was excellent with only two (0.2%) missed doses out of 1042 injections given. Two patients also delayed one dose each (<12 h).

Our pilot RCT demonstrated that a trial assessing the effect of extended perioperative thromboprophylaxis using tinzaparin on disease-free survival in patients with resectable colon cancer is feasible and well tolerated. A large multicenter RCT evaluating this question is currently enrolling at Canadian centers.

Our rate of recurrent disease is lower than previously published summary estimates [14]. This discrepancy may be due to our small number of included patients and the short follow-up period. Eighty percent of the recurrences of colon cancer occur in the first 3 years [14]. Disease-free survival at 3 years has been previously reported to be 66% for this patient population. Furthermore, the correlation between 3-year disease-free survival and 5-year overall survival was 0.89 [14]. Hence, disease-free survival at 3 years will be the primary outcome of the full-scale trial.

Low molecular weight heparin has been shown to improve cancer-specific survival and prevent VTE in cancer patients [4,15]. Mechanistic studies suggest that surgical stress promotes a pro-metastatic state [8]. LMWHs, specifically tinzaparin, seem to inhibit the development of cancer metastases [16]. Furthermore, a retrospective post-hoc analysis of a study assessing adjuvant razoxane in patients that underwent curative surgery for colorectal cancer showed that the use of perioperative unfractionated heparin was associated with an improvement in the 5-year overall and disease-specific survival [17]. If extended perioperative thromboprophylaxis with tinzaparin can decrease metastatic spread and improve disease-free survival in patients with resectable colorectal cancer; this would improve the health and quality of life for patient with otherwise limited disease.

It is important to note the limitations of our trial. First, we did not perform a double-blind RCT and our results may be subjected to bias. An open RCT design was chosen in order to optimize feasibility and avoid for patients to have to self-inject placebo for an extended period of time. However, we tried to minimize bias by ensuring adequate sequence generation and allocation concealment. Second, the total number of disease recurrence, major and minor bleeding episodes was small. Larger studies are needed to provide more reliable estimates. Finally, a large proportion of patients refused consent (56%). Patients who refused consent frequently reported that they felt overwhelmed at their first surgical visit or that they were not interested in self-injection. However, once enrolled, patient compliance was excellent.

In conclusion, a RCT investigating the effect of extended perioperative thromboprophylaxis using tinzaparin on disease-free survival in patients with resectable colon cancer is needed, feasible and well tolerated. A large multicenter RCT evaluating this question is currently on-going.

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## Conflicts of interest

There are no conflicts of interest.

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## Thrombotic thrombocytopenic purpura associated with statin therapy

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Acquired thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease with an annual incidence of approximately six per million in the UK. More than 70% of cases are idiopathic but secondary TTP may be precipitated by pregnancy, infections such as HIV, pancreatitis or drugs [1].

The thienopyridine-derivatives ticlopidine and clopidogrel are two of the most common drugs associated with TTP in the US Food and Drug Administration safety databases [2]. However, in the original case series describing clopidogrel-associated TTP, five out of the eleven patients were on simvastatin or atorvastatin, two of whom had begun the drug within 3 weeks of TTP onset [3]. One patient had discontinued clopidogrel and started atorvastatin 3 weeks before TTP. Another patient had a recurrence after receiving atorvastatin for 14 days. In the subsequent expanded case series, 10 out of 37 patients apparently developing TTP after clopidogrel were also taking a statin [4].

Statins are competitive antagonists of the enzyme HMG-CoA reductase, which are increasingly recognized to have effects beyond their lipid-lowering ability, such as maintaining plaque stability and modulating both endothelial function and inflammatory responses. They are in widespread use in the West and it has been estimated that over 7 million people in the UK are on a statin, with 48.5 million prescriptions issued in 2008 (NHS Information Centre). There have been two previous case reports of TTP associated with simvastatin treatment in absence of antiplatelet agents [5,6].

We report three cases of possible statin-associated TTP seen in our department between 2004 and 2009. Median patient age was 58 (51–61 years) and all patients were men. Forty-eight cases of TTP were seen in our department in patients over 50 years of age during this period. Statin use is more common in older people, whereas TTP predominantly affects younger patients, particularly women [1]. There were no cases of clopidogrel-associated TTP during this period. Clinical and laboratory features are shown in Table 1.

The patients had typical clinical presentations of TTP: one had fever and two had neurological symptoms. Patient B had started simvastatin 40 mg 1 month before presentation; patients A and C had their statin dose increased within the previous month. There were no

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Table 1 Clinical and laboratory features at presentation

	Patient A	Patient B	Patient C
Age/sex	51 M	61 M	58 M
Past medical history	Type 2 diabetes; hypercholesterolaemia	Hypercholesterolaemia	Hypercholesterolaemia; psoriasis
Statin dose	Simvastatin 40 mg	Simvastatin 40 mg	Atorvastatin 20 mg
Time on statin (days)	145	30	98
Dose increase (weeks)	4	–	<2
Concurrent medication	Metformin	Nil	Calcipotriol cream
Clinical features at admission (duration in days)	Fever, myalgia, lethargy, flank pain, jaundice, dark urine (7d)	Headache (7 d); Confusion + agitation (1 d)	Intermittent facial + L forearm numbness (10 d); Dysphasia, headache (2 d)
Hb g/dl	8.4	5.1	10.1
Platelets × 10 <sup>9</sup> /dl	12	18	36
LDH iu/l (NR 240–480)	2443	3518	1907
Creatinine μmol/l (NR 66–112)	105	86	115
Troponin T (NR<0.01)	<0.01	0.09	–
ADAMTS 13 activity (NR 66–126%)	13 (<5 mixing)	<5	<5
Anti ADAMTS13 IgG (NR<4%)	34	44	5.6

ADAMTS13, a disintegrin-like and metalloprotease with thrombospondin type 1 repeats.

other obvious precipitants, including antiplatelet agents. All patients had microangiopathic haemolytic anaemia, thrombocytopenia, reduced ADAMTS13 activity by collagen binding assay and anti-ADAMTS13 immunoglobulin G (IgG) by in-house enzyme-linked immunosorbent assay.

The median number of plasma exchanges to remission was 13.5 (range 5–22.5 plasma volumes). All patients received methylprednisolone (0.5–1 g intravenously for 3 days) and patients A and B also received rituximab (375 mg/m<sup>2</sup> weekly for four doses). There were no long-term complications. Significantly, reintroduction of atorvastatin in remission in patient C led to a fall in platelet count to 80 3 weeks later associated with a reduction in ADAMTS13 activity (<5%), which responded to just a single plasma exchange and cessation of the statin. There were no other relapses.

In conclusion, simvastatin and atorvastatin, especially at higher doses, appear associated with an acute TTP presentation and may explain some of the cases of TTP previously attributed to clopidogrel. This may not be a class effect, as pravastatin sodium was subsequently used in patient B with no evidence of relapse and has been used safely in other of our TTP patients. The reason for this difference is unclear as pravastatin is classified as a type 1 statin (substituted decalin-ring structure) like simvastatin, whereas atorvastatin is a type 2 statin (fully synthetic with a larger group linked to the HMG-like moiety). It is, however, recognized that different statins have slightly varying side-effect profiles. The mechanism in these cases appears to be immune-mediated ADAMTS13 deficiency, with all patients having detectable anti-ADAMTS13 IgG. The poor correlation between anti-ADAMTS13 IgG titre and ADAMTS13 activity is often seen and reflects the presence of noninhibitory antibodies [7] or their differing inhibitory potential.

By contrast, more recent evidence suggests ADAMTS13 activity is preserved in clopidogrel-associated TTP and

the toxicity may result from endothelial cell injury or stimulation [2,8]. From the South East England TTP Registry, which reported 236 acute episodes [1] and the UK TTP registry (accruing 100–150 acute episodes per year), we have no documented association of TTP with clopidogrel. A careful drug history should be taken in all patients at presentation of TTP, and patients who have a history of TTP should avoid therapy with simvastatin and atorvastatin for hypercholesterolaemia.

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### Conflicts of interest

There are no conflicts of interest.

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