Gastrointestinal Cancer: Targets and Therapy

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REVIEW

Optimal management of venous thromboembolism in advanced pancreatic cancer with low–molecular-weight heparin: current evidence

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Abstract: Former evidence delineates a strong correlation between cancer and venous thromboembolic events (VTEs). Of all the malignancies, pancreatic cancer confers the highest risk for developing VTE during the course of the disease. The role of primary thromboprophylaxis in the comprehensive treatment of pancreatic cancer remains unclear. We have conducted a systematic review to assess the role of primary thromboprophylaxis in pancreatic cancer. Literature searches included PUBMED, EMBASE, Cochrane Library, and the database of clinical trials in order to identify relevant publications. Seven publications that included 6,003 patients were analyzed in our systematic review. The systematic review of current literature indicates that thromboprophylaxis reduces the risk of VTE without increasing the risk of major bleeding. However, data regarding survival benefits are inconclusive.

Keywords: low-molecular-weight heparin, pancreatic cancer, thrombophylaxis

Introduction

Cancer is highly associated with increased risk for venous thromboembolic event (VTE), as reported first by Trousseau >150 years ago.[1] Furthermore, various studies have demonstrated that cancer augments VTE risk by sevenfold, with pancreatic cancer (PC) being an additional risk factor.[2,3] Sproul et al were the first to report a relationship between PC and thrombosis, documenting a 60% prevalence of venous thrombosis during autopsy, compared to 20%–25% in other malignancies. It has been suggested that the risk of VTE is closely related to the tumor biology, in terms of not only the metastatic course but also tumor grade and proliferation index. Of all the solid tumors, the highest rate of VTE has been noted in PC, while the prevalence of VTE ranges from 4.1% to 12.1% in different trials.[4–6]

The majority of patients with PC are diagnosed with metastatic disease. The presence of metastatic disease is strongly associated with an increased risk for VTE. An analysis of the data in the California Cancer Registry demonstrates that regardless of cancer type, the incidence of VTE is higher in patients with metastatic disease at the time of diagnosis.[7]

The course of PC is often complicated with thromboembolic events. Lower-extremity deep venous thrombosis, thrombophlebitis migrans, and pulmonary embolism (PE) are among the well-known manifestations of VTE in PC patients. Further disorders also include disseminated intravascular coagulation, splenic vein

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thrombosis, portal or superior mesenteric vein thrombosis, spontaneous arterial thromboembolism, extremity ischemia, and mesenteric or iliofemoral occlusion.[8–11] Cancer therapy (surgery, chemotherapy, and hormonal therapy) serves as an additional risk factor for developing VTE. According to a retrospective analysis of the Prophylaxis of Thromboembolism During Chemotherapy (PROTECHT) study,[12] in the absence of thrombophylaxis, the highest risk of thrombosis is seen in patients receiving gemcitabine (8.1%) or cisplatin-based chemotherapy (7%). The combination of both drugs increased the risk to up to 10%. Because gemcitabine represents a major therapeutic alternative in PC, it may induce further risk for VTE.[12] According to the MicroTec study,[13] circulating tissue factor-bearing microparticles are associated with a higher risk of VTE. Thromboprophylaxis with low-molecular-weight heparin (LMWH) in patients with high levels of tissue factor-bearing microparticles significantly reduces VTE.[13]

In addition to chemotherapy, supportive care measures used in cancer patients may enhance the risk of VTE. The use of colony-stimulating hormones such as erythropoietin for treating symptomatic anemia has been associated with an increased risk of VTE. A meta-analysis of 35 studies reported that the use of epoetin or darbepoetin increases the risk of TEs by ~67% compared to patients not receiving these agents.[14] Sorensen et al[15] have reported an inferior overall survival in patients with cancer and VTE. This finding has been further confirmed in PC, which is associated with a diminished overall survival when diagnosed synchronous with VTE. The overall survival is even worse when the VTE occurs during the course of chemotherapy.[15] Several studies have evaluated the efficacy and safety of LMWH as primary thromboprophylaxis for VTE in cancer patients, indicating contradictory results. Prophylaxis was associated with a statistically significant reduction of TEs; however, survival benefit was not documented. Therefore, most current guidelines do not endorse the routine use of thromboprophylaxis. Nevertheless, some guidelines do support considering primary thromboprophylaxis on a case-by-case basis in highly selected outpatients with solid tumors receiving chemotherapy.[16]

The rationale for incorporating LMWH into practice originates not only from the antithrombotic prospect but also from the putative antineoplastic traits of these drugs. It has been shown that patients treated with long-term anticoagulant therapy have a relatively low incidence of cancer.[17–19] A few reports have demonstrated tumor regression, suggesting the potential for antineoplastic activity of LMWH.[20–22] Therefore, LMWH has been adopted as a favorable anticoagulant in cancer patients with VTE.

Methods

Data sources

We searched the following databases: Cochrane Central Register of Controlled Trials, published in The Cochrane Library; PubMed (1966–March 2016); the database of clinical trials in cancer patients; conference proceedings of the American Society of Clinical Oncology (1995–March 2016) and American Society of Hematology (2006–March 2016); proceedings of the European Society of Medical Oncology (ESMO) (2006–March 2016) and the European Hematology Association (2006–March 2016); as well as the databases of ongoing and unpublished trials (http://www.clinicaltrials.gov and http://www.clinicaltrials.nci.nih.gov). The terms (pancreas OR pancreatic) AND (tumor OR malign * OR carcinoma * OR cancer) AND (heparin OR low-molecular weight heparin OR enoxaparin OR dalteparin OR reviparin OR certoparin OR tinzaparin OR bemiparin OR nadroparin OR *parin) AND (thromboembolism) were used for the searches.

Results and discussion

Thrombophylaxis in PC

Key clinical trials

The characteristics of the randomized controlled trials (RCTs) that enroll PC patients for primary thrombophylaxis (as the target population or partially) are presented in Table 1.

LMWH as primary thrombophylaxis in PC

Several RCTs have appraised primary thromboprophylaxis in ambulatory cancer patients.[23] Two of these trials evaluated the benefit of primary thrombophylaxis in PC only. The PROSPECT-CONKO 004,[24] a prospective, randomized trial enrolled PC patients to receive chemotherapy plus enoxaparin or chemotherapy only. The primary end point was the incidence of VTE. Thromboprophylaxis was given through the first 12 weeks of treatment. Enoxaparin was associated with a relative risk reduction of 60% (15.1% VTE in the control group and 6.4% in the enoxaparin group) in VTE, with no increased risk of bleeding events between the two groups. However, no difference was detected between the two arms for the secondary end points of overall survival and progression-free survival.[24]

An RCT of dalteparin in patients with advanced PC (the UK-FRAGEM study)[25] which randomized 123 patients with advanced PC to receive either gemcitabine with weight-adjusted dalteparin (GEM-WAD) for 12 weeks or gemcitabine (GEM) alone, indicated a significant reduction

Table 1 Summary of all available studies on thromboprophylaxis with LMWH in pancreatic cancer patients

First author, year (trial)	Design	LMWH, schedule	Duration of treatment	Number of patients	Concomitant therapy, cancer type	Pancreas,%	VTE	Survival
Kakkar et al, 2004[26] (FAMOUS)	Prospective, multicenter RCT	Dalteparin (5,000 IU, sc, od); control: placebo	1 year	196 LMWH, 189 control	Breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary, or uterus	LMWH: 9.5%; control: 13%	LMWH: 2.4%; control: 3.3%	1 year; LMWH: 46%; control: 41%
Klerk et al, 2005[29]	RCT	Nadroparin: received body weight-adjusted therapeutic doses of sc nadroparin for 2 weeks (<50 kg, 3,800 IU twice daily; 50–70 kg, 11,400 IU od; >70 kg, 15,200 IU od), followed by half-therapeutic doses for an additional 4 weeks (<50 kg, 3,800 IU od; 50–70 kg, 5,700 IU od; >70 kg, 7,600 IU od)	6 weeks	148 LMWH, 154 control	Solid cancers	LMWH: 5%; control: 6%		
Agnelli et al, 2009[27] (PROTECHT)	Prospective, multicenter RCT	Nadroparin (3,800 IU sc, od); control: placebo	Duration of chemotherapy or up to a maximum of 120 days	779 LMWH; 387 control	Gastrointestinal, pancreatic, breast, ovarian, or head-and-neck cancer	LMWH: 4.7%; control: 4.5%	LMWH: 8.3%; control: 5.9%	NR
Pelzer et al, 2015[24] (CONKO-004)	RCT, open label	Enoxaparin (1 mg/kg, sc, od); control: no enoxaparin	12 weeks	160 LMWH; 152 control	Pancreatic cancer	100.00%	LMWH: 6.4%; control: 15.1%	LMWH: 31 weeks; control: 29 weeks
Van Doormaal et al, 2011[28]	RCT	Nadroparin: received body weight-adjusted sc therapeutic doses for 2 weeks (<50 kg, 3,800 IU twice daily; 50–70 kg, 11,400 IU od; >70 kg, 15,200 IU od), followed by half-therapeutic doses for an additional 4 weeks (<50 kg, 3,800 IU od; 50–70 kg, 5,700 IU od; >70 kg, 7,600 IU od)	12 weeks	244 LMWH; 259 control	Prostate, lung, and pancreatic cancer	LMWH: 26%; control: 28%	NR	LMWH: 8 months; control: 10.4 months
Maraveyas et al,[25] 2012	RCT	Dalteparin 200 IU/kg sc, od, for 4 weeks, followed by a step-down regimen to 150 IU/kg for a further 8 weeks); control: no dalteparin	12 weeks	63 LMWH; 60 control	Pancreatic cancer	100.00%	LMWH: 3%; control: 23% (WAD period: <100 days)	LMWH: 8.7 months; control: 9.7 months
Agnelli et al, 2012[30] (SAVE ONCO)	RCT	Semuloparin, 20 mg, sc, od	3.5 months (median), until change of chemotherapy	1,608 LMWH; 1,604 control	Lung, pancreatic, gastric, colorectal, bladder, and ovarian cancer	LMWH: 8%; control: 8%	LMWH: 2.4%; control: 10.4%	NR

(*Continued*)

Table 1 (*Continued*)

First author, year (trial)	Design	LMWH, schedule	Duration of treatment	Number of patients	Concomitant therapy, cancer type	Pancreas,%	VTE	Survival
Zwicker et al, 2013[13] (MICROTEC)	RCT – Phase II	Enoxaparin 40 mg, od	60 days	23 LMWH; 43 control	Pancreatic, non-small-cell, and colorectal cancer	LMWH: 48%; control: 54%	LMWH: 5.6%; control: 27.2%	LMWH: 17.8 months; control: 11.8 months
Saroj Vadhan-Raj, MD Anderson Cancer Center (www.clinicaltrials.gov)	RCT	Dalteparin 5,000 units, sc, by injection under the skin, daily for 16 weeks	16 weeks	NR	Pancreatic cancer	NR	NR	NR
James Roach, Momenta Pharmaceuticals (www.clinicaltrials.gov)	RCT – Phase I/II	M402 (necuparanib)	ongoing	ongoing	ongoing	Ongoing	ongoing	ongoing

Note: Overall survival is based on tissue factor-bearing microparticle status.
Abbreviations: LMWH, low-molecular-weight heparin; NR, not reported; od, once daily; RCT, randomized controlled trial; sc, subcutaneous; VTE, venous thromboembolic event; WAD, weight-adjusted dalteparin.

of all-type VTE. During the WAD treatment period, VTE was reduced from 23% to 3.4%, and all-type VTE throughout the follow-up period was reduced from 28% to 12%. "Lethal VTE" (events that clinically or postmortem were referred to as the cause of death) during the first 100 days was documented only in the control arm. There were fewer severe hemorrhagic complications in the GEM-WAD arm; however, trivial bleeding, mostly skin bruising and minor epistaxis, occurred in the GEM-WAD arm (9% vs 3%). Tumor control rates were similar between the two groups; median overall survival was 9.7 months for the GEM group and 8.7 months for the GEM-WAD group (P=0.841) and time to progression (TTP) was 5.3 months and 5.5 months, respectively (P=0.841).[25]

LMWH as primary thrombophylaxis in various malignancies, with PC as a subgroup

Several RCTs have evaluated LMWH concomitantly with chemotherapy in a variety of advanced solid malignancies. In the FAMOUS trial,[26] dalteparin was not found to have a significant impact on the risk of VTE compared with placebo in patients with advanced cancer, nor did it have an impact on survival. PC patients comprised 9.5% of the interventional group and 13% of the placebo group.[26] In the PROTECHT trial,[27] ambulatory patients were randomized to receive nadroparin or placebo for the duration of chemotherapy up to a maximum of 4 months. Among 1,150 patients, 53 (4.7%) had PC. In contrast to other trials, in the PROTECHT trial,[27] VTE rate was higher in the experimental group (8.3% vs 5.8%), possibly due to a small sample size. No data were reported on overall survival or TTP.[27] Another trial that randomized patients to receive nadroparin in addition to chemotherapy showed that there was no effect on survival or TTP. The median time to survival in the nadroparin and control arms was 8 months and 10.4 months, respectively. TTP in the nadroparin group was 5.7 months vs 6.7 months in the control group.[28] On the contrary, Klerk et al[29] showed that a brief course of nadroparin had a favorable impact on survival in patients with advanced tumors. In this trial, patients were assigned to receive nadroparin or placebo for 6 weeks during the beginning of their chemotherapy course. PC patients comprised 5% of the study's sample. The survival benefit was greater in patients with an expected survival of ≥6 months at enrollment, with a hazard ratio of 0.61 (95% confidence interval [CI]: 0.42–0.89), compared to a hazard ratio of 0.82 (95% CI: 0.51–1.29) in patients with life expectancy <6 months.[29]

In the SAVE ONCO trial,[30] 3,212 patients with solid tumors were randomized to receive semuloparin, an ultra-LMWH, or placebo with the chemotherapy regimen, until a change of the chemotherapy occurred; 8% of the patients had PC. Semuloparin was associated with a reduction in the risk of deep vein thrombosis (DVT) and fatal and nonfatal PE for the entire study population. In the PC subgroup, VTEs were reduced from 10.9% to 2.4% in the semuloparin group. Semuloparin did not influence the overall survival of all cancer types.[30] A meta-analysis of all randomized trials performed by our group evaluated the impact of prophylactic LMWH on preventing VTE as

well as the impact on survival.[31] We assessed the risk for DVT and PE; LMWH significantly reduced symptomatic DVT (relative risk [RR]: 0.35; 95% CI: 0.21–0.61) and PE (RR: 0.49; 95% CI: 0.25–071). In a subgroup of patients with PC, a pronounced effect of LMWH on VTE reduction has been documented (RR: 0.31; 95% CI: 0.18–0.55).The risk of major bleeding was not significantly increased. Our meta-analysis did not depict a survival advantage; however, in some of the included studies in an individual subgroup analysis, the group of patients with better prognosis experienced superior survival[26,29]

Current guidelines and recommendations

The American Society of Clinical Oncology,[32] the National Comprehensive Cancer Network,[33] and the ESMO[34] have developed guidelines for VTE prophylaxis in patients with cancer. The primary goal of thromboprophylaxis is VTE prevention, including PE and early death resulting from these complications. All guidelines recommend the use of prophylactic anticoagulation in hospitalized cancer patients unless contraindicated. All guidelines do not support routine primary thromboprophylaxis for ambulatory cancer patients outside clinical trials. Thromboprophylaxis may be considered in high-risk patients with a Khorana score ≥3. The Khorana score is a validated risk score used to identify patients at risk of VTE during chemotherapeutic treatment. It comprises patient characteristics such as cancer type and prechemotherapy blood counts. PC grants the patients with an additional two points, translating into a very high risk for VTE from the time of diagnosis.[6] Based on current guidelines, anticoagulation should not be used to improve survival in cancer patients in the absence of other indications.

Conclusion

VTE is a notable complication of cancer and cancer treatment, which causes considerable morbidity and mortality. As hospitalized and surgical patients with cancer are at higher risk for VTE, thrombophylaxis should be considered in this setting. Nevertheless, its role in ambulatory patients remains to be elucidated. PC patients are a unique subgroup of patients, due to relatively aggressive biological traits such as high incidence of VTE, hence making this therapeutic option more appealing. Most trials show a significant reduction of VTE in PC without a great risk of major bleeding. While the role of primary thrombophylaxis in cancer patients remains unclear, future studies, some of which are ongoing, might shed a light on its impact in the subset of the highly thrombogenic PC. The use of surrogate predictive biomarkers such as circulating tissue factor-bearing microparticles, as seen in the MicroTec trial,[13] may further optimize our understanding for the finest patient selection for this treatment.

Disclosure

The authors report no conflicts of interest in this work.

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