Pancreatic Disorders & Therapy
ISSN: 2165-7092

Maraveyas and Muazzam, Pancreat Disord Ther 2015, 5:1
DOI: 10.4172/2165-7092.1000e137

Editorial Open Access

Thromboprophylaxis in Pancreatic Cancer: Why isn't Prime Time Here Compared to Multiple Myeloma?

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Rec date: Mar 23, 2015; **Acc date:** Mar 25, 2015; **Pub date:** Mar 27, 2015

Editorial

Hypercoagulability and the clinical manifestation of VTE are shared by most cancers and the use of chemotherapy canfurther increase this risk. VTE in cancer patients results in increased morbidity and mortality [1]. Patients with advanced pancreatic cancer (APC) have one of the worst prognoses of all malignancies and the highest incidence of disease provoked venous thromboembolism (VTE) [2]. Given the prominence of VTE in APC, it is not surprising that data on VTE prevention for APC have been generated from subgroup analysis of non-APC targeted placebo-controlled randomized trials of cancer patients treated with chemotherapy. Further data is derived from trials dedicated to evaluate VTE prophylaxis in APC patients. These studies have been rather homogeneous in that only low molecular weight heparins (LMWH) have been investigated for anticoagulation. The choice of LMWH was partly industry driven (e.g. study of new agent such as the semi-synthetic LMWH semuloparin) and partly due to the established superiority of LMWH over vitamin K analogues in terms of safety and efficacy both in VTE prophylaxis when given in non-oncologic settings and in the therapeutic (treatment) settings of malignancy associated established VTE [3].

SAVE-ONCO and PROTECHT are the largest trials that enrolled between them more than 4000 patients with non-selected solid cancers using LMWH for the variable length of palliative chemotherapy. Both studies showed similar reduction in the symptomatic venous thrombosis (DVT) and non-fatal pulmonary embolism (PE) and in the case of SAVE-ONO, arterial thromboemoblic events were also decreased. There was a subgroup of around 300 APC patients in both of these trials but benefit in APC subgroup was only seen in SAVE-ONCO study. While the VTE reduction for the whole patient population (primary aim of the study) was from 3.9% to 2%, it went from 10.9% in the placebo arm to 2.4% in the LMWH arm for the APC subgroup [4,5]. Two trials evaluated VTE prevention by enrolling APC patients only who were receiving gemcitabine based first line palliative chemotherapies. These studies randomized over 400 APC patients equally into LMWH or placebo. CONKO 004 showed that the use of enoxaparin at an unconventionally (high) primary prophylaxis dose of 1 mg/kg reduced the incidence of symptomatic (DVT and PE combined) from 9.87 to 1.25% [6]. FRAGEM had a broader primary endpoint of all-type VTE (i.e.DVT/PE but also incidental PE and arterial and splanchnic VTE), [2] and an "even higher" dose of LMWH (dalteparin at 150-200 u/kg) was used. It showed a significant 85% risk reduction in all-type VTE in the dalteparin arm as compared to placebo (3.4% vs. 23%) over the 3 months of thromboprophylaxis [7]. None of these studies increased risk of major bleeding significantly and no fatalities were noted in APC due to haemorrhage in either of these RCTs. Subsequent meta-analysis of these trials have verified the significant impact of thromboprophylaxis on APC related VTE [1].

Up to a quarter of APC patients die within the first 3 months of diagnosis. This early death burden (EDB) in APC is partly due to progressive cancer and rather less to treatment related consequences. Multiple autopsy series in APC confirm that undetected VTE also contributes to EDB significantly. This hypothesis was further supported by findings from the FRAGEM trial whereby during the first 3 months of treatment period, 3 out of 4 deaths observed in the placebo arm were secondary to VTE. On the other hand, there was only 1 death in the treatment (dalteparin) arm during this duration and this was a result of sepsis rather than thrombosis [7]. In the later period of study, (beyond 3 months) the vast majority of deaths occurred due to progressive disease. Similar trend was seen in the early analysis of the EPIPHANY trial which is an observational study of cancer patients developing PE and treated in the outpatient settings. In the first 3 months, 56% deaths were related to cancer progression but PE related (PE and other causes) deaths were observed in 47% patients [8].

Despite clear association between the development of VTE in APC patients and the risk of death, neither CONKO 004 nor FRAGEM had shown any improvement in overall survival [6,7]. This is certainly due to the competing risk of death in APC which precludes the beneficial survival impact from VTE prevention being observed [9]. It means that even if LMWH is preventing VTE related deaths in APC during the first 3 or 6 months of their chemotherapy treatment, patients will still inevitably die from swift cancer progression making it difficult or even impossible to detect any survival advantage from VTE prophylaxis in this setting. In other words, survival due to VTE prophylaxis in APC will manifest only when we are able to use very effective anti-cancer agents and strategies [just like recently seen in multiple myeloma (MM)] which will delay deaths due to cancer progression and result in prolonged patient survival. With death burden due to cancer progression significantly reduced or out of the equation, strategies of VTE prophylaxis may add to potentially significant longevity of these patients by preventing VTE related early cancer deaths. Another therapeutic approach would be to use VTE prophylaxis in the adjuvant settings where similar considerations apply – i.e. Impact on survival curves of VTE related death of potentially cured patients [10].

Despite these data, the only indication for VTE prophylaxis in ambulatory cancer patients recommended by the Italian Association of Medical Oncology (AIOM), the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), the French National Federation of the League of Centers Against Cancer (FNCLCC) and the European Society of Medical

Oncology (ESMO) is in MM patients when they are treated with immuno-modulators (iMiD) or with chemotherapy using high doses of steroids [11]. Only the International thrombosis society guidelines recommend the use of VTE prophylaxis in high risk ambulatory APC patients who are getting treatment with chemotherapy. This is despite that these societies and networks recognizing that not only are APC patients at the highest risk of VTE among all cancers but they also gain maximum benefits from preventive strategies against VTE [12].

Indeed before the clinical availability of iMiD and proteasome inhibitors (PI), patients with MM had one of the lowest incidences of malignancy related VTE. These novel agents improved the median survival from 2 to 3 years to 5 to 7 years [13] and variably affected the risk of VTE in MM patients. IMiD increased the incidence of VTE to 25% (inducers of thrombosis) but the risk was reduced to 4% with PI use (protective against thrombosis). LMWHs, which were used in a non-randomised manner in trials assessing the efficacy of iMiD in the setting of MM suggested significant benefit with reduction of risk of VTE from 24 to 3% when used with thalidomide and 15% to 5% when used with lenalidomide. Bleeding risks were acceptable [14]. Subsequently 2 large randomized trials compared aspirin, warfarin and LMWH in a low risk for VTE setting and all 3 agents were found protective. It was felt unethical to include a placebo arm even in these low risk trials, so the likelihood of the question ever being asked in an RCT for high risk MM patients is nil [15]. There is suggestion that VTE has no impact on survival of myeloma patients in the first 6 months of diagnosis. Only arterial thrombosis which was seen in 5.6% of MM patients was associated with inferior survival [16]. However the early survival deficit seen in a trial of high dose dexamethasone and iMiD compared to the low dose dexamethasone iMiD arm (despite a much improved response rate in the high dose arm) did raise concerns that some of these patients may have experienced undiagnosed lethal VTE [17,18].

This disparity in the guidelines for patients with multiple myeloma and APC is difficult to understand. Recommendations for thromboprophylaxis of MM patients appeared in these guidelines before any randomised trial was ever done and based on the data that cumulatively had fewer patients studied than the above mentioned trials in APC. This widespread acceptance of VTE prophylaxis in MM and the absence of such recommendations for APC may reflect the greater sensitivity towards VTE among the haematologists than that shown by the oncological community. Patients with haematological malignancies always get more pro-active and aggressive care than patients with solid cancers even in their end of life [19]. Despite the introduction of new combination chemotherapies, median survival of patients with APC remains less than 1 year. Patients with pancreatic cancers remain unfortunate in that despite eligibility, many patients are not offered radical treatments even at early stages of diagnosis [20]. Therefore it is not surprising that these patients are declined VTE prophylaxis by the attending physicians at their advanced stages. There is a lack of the 'potential cure' aura of cancer treatment here.

There is good evidence to support the above downhearted assertion. We have studied the attitudes of doctors prescribing therapeutic LMWH for established VTE and described the challenge for physicians when treating advanced cancer patients due to shorter life expectancy, risk of bleeding and discomfort of frequent (self-) injections [21]. Decisions are often made without the consultation of the patient. Their short survival influences the attitudes of treating physicians when they are deciding about VTE treatment or prophylaxis despite its known benefits. The paternalistic attitude of physicians in these 'hopeless' cancers where short term palliation is the maximum on offer from the cancer treatment can be summed up by the phrase ' A PE is a nice way to go' [22]. The same investigators that extensively probed this attitude have also demonstrated that patients are given comprehensive education and written material about other cancer related complications (some of which happen in less than 1% of patients) but the issue of cancer associated thrombosis is not discussed. This can also result in delay of identification of red flag symptoms of thrombosis to the detriment of overall quality of life and impact on the cancer treatment itself [23]. It stands to reason therefore that few pancreatic cancer patients at the beginning of their chemotherapy journey, if they have not already presented with a VTE, will be told that they have a one in 4 chance of developing this condition in the next 6 months of their lives. It is equally unlikely that they are told that this is a largely preventable condition.

Not implementing VTE prophylaxis on the basis on the often articulated argument that the beneficial effect has a rather narrow health economic impact or is expensive makes little sense. Many implemented interventions in oncology have narrow health economic impacts [24]. For many the only benefit is to provide an improved quality of life (QoL). In APC, gemcitabine became the standard of care in the late 90s despite being much more expensive than 5-FU mostly because of this type of benefit [25]. Although a prospective health economic study in APC thrombo-prophylaxis as part of an RCT has not been done, cost-analysis study of medical claims data has shown that cancer patients with VTE use significantly more health care resources during their first 12 months post diagnosis while on chemotherapy compared with cancer patients without VTE. Within this study the highest health utilization resource group was patients with pancreatic cancer at $17205 compared to $10297 and $8301 for ovarian and colorectal cancers respectively [26]. This does not take into account the rather stark differences in median survivals between these groups. In terms of the argument of the burden of self-injection we have recently shown that the patients' priorities are totally different to what is intuitively articulated by the clinical community. In a qualitative study using conjoint methodology of a cohort of 100 cancer patients receiving long term either oral or self-injected anticoagulation 39% prioritized 'minimal interference with their cancer treatment' followed by treatment efficacy (24%) and low risk of adverse event (19%). Only 13% demonstrated preference of oral over injection [27].

Even among cancer survivors, patients with multiple myeloma and pancreatic cancer have got the worst health-related (physical and mental) QoL [28]. Development of VTE in cancer patients can further compromise their QoL [29]. Between patients with APC and MM, APC has the worst prognosis with more symptom burden and shorter survival. Therefore these patients deserve particular emphasis on best supportive management especially those which will improve their QoL [30]. While most first line palliative chemotherapies in APC are known to stabilize QoL, the numbers of patients benefiting from these treatments are limited and second and third line treatments show no significant improvement in this global QoL [31]. Therefore in APC patients, balancing the trade-offs between QoL and survival takes priority [32]. We agree with the recommendations of using VTE prophylaxis in patients with MM getting treated with IMiD but at the same time, we believe that APC patients have an equally strong case for thromboprophylaxis. These patients have inherently very high risk for VTE even without chemotherapy use. Prevention of thrombosis in APC will lead to at least one less problem in the short lifespan of these unfortunate patients. It should be part of their supportive regimen to improve their QoL irrespective of whether they are on active

pharmacologic treatment or they are candidates for best supportive care.

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