JOP. J Pancreas (Online) 2013 Mar 10; 14(2):135-137.

HIGHLIGHT ARTICLE

Thromboembolism and Anticoagulation in Pancreatic Cancer

Highlights from the "2013 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 24-26, 2013

Muzzamal Habib[1], Muhammad Wasif Saif[2]

[1]St. Elizabeth's Medical Center and [2]Tufts Medical Center. Boston, MA, USA

Summary

Pancreatic cancer is a hypercoagulable condition, and venous thromboembolism affects up to 17% to 57% of pancreatic cancer patients. Initiating chemotherapy further increases the risk. For cancer patients initiating chemotherapy, there is currently no approved treatment for the primary prevention of venous thromboembolism risk. The authors summarize the two abstracts (#151 and #284) presented at the 2013 ASCO Gastrointestinal Cancers Symposium which were focused newer treatment options and the incidence of thromboembolism in pancreatic cancer patients especially in East Asian patients. Additionally the authors review the risk of thrombosis associated with the chemotherapy and erythropoiesis stimulating agents and its prognostic implications and possible managements.

What We Knew Before the 2013 ASCO Gastro-intestinal Cancers Symposium?

Pancreatic cancer is known to be associated with thromboembolism. Shaib *et al*. reported incidence of thromboembolism in upto 28.9% of pancreatic cancers patients [1]. In a systematic analysis thromboembolic event in pancreatic cancer patients predicted excess premature (3 months) mortality [2]. The pathogenesis of hypercoagulability in cancer is multifactorial: increased expression of pro-thrombotic factors (tissue factor, thrombin and fibrinogen), decreased inhibitors of anticoagulation and an increase in platelet aggregation resulting from increased fibrinogen, thrombospondin I and mucin [3, 4, 5, 6, 7, 8]. In addition, chemotherapy is associated with about 5 times increased risk of thromboembolism [3]. This higher incidence of thromboembolism is compounded further with the use of erythropoietin based therapies [4].

Despite all the advances in treatment modalities including better surgical techniques and newer chemotherapeutic agents, the associated morbidity and risks are high and prognosis remains poor, with reported 5-year survival of only 2-4%. It highlights the need for better and newer treatment options. In terms of risk of thromboembolism there has been attempts to use low molecular weight heparin in this patient population with no contraindications to low-molecular-weight heparin when on chemotherapy and hospitalized. There are no definite guidelines for ambulatory patients. The Eastern Cooperative Oncology Group (ECOG 8200) conducted a randomized phase II trial of irinotecan/docetaxel, with or without cetuximab, in metastatic pancreatic cancer. Patients not receiving therapeutic anticoagulation received enoxaparin 40 mg/day. The results showed that the routine use of prophylactic low molecular weight heparin is feasible in patients with advanced pancreatic cancer, with a low risk of hemorrhage in study [5]. Progression free survival was 3.9 months in patients with baseline thrombosis versus 4.2 months in patients with no thrombosis. A European study, Charité Onkologie (CONKO)-004 trial, randomized patients with advanced pancreatic cancer to chemotherapy alone *versus* simultaneous low-molecular-weight heparin (1 mg/kg once a day for 3 months, followed by 40 mg daily) and chemotherapy. There was a significant decrease in the incidence of symptomatic venous thromboembolism in the treatment *vs*. no treatment arm after 3 months (1.25% *vs*. 9.87%, respectively) as well as after 12 months (5.00% *vs*. 15.13%, respectively). There was no significant difference in major bleeding in both arms. The median follow up time was 45.44 months. There was no significant difference in median time to progression (5.03 months in the treatment arm *vs*. 5.42 months in no treatment arm; P=0.941) or median overall survival (7.92 months in treatment arm *vs*. 8.15 months in no treatment arm; P=0.054) [6].

Key words Carcinoma, Pancreatic Ductal; Venous Thrombo-embolism

Correspondence Muhammad Wasif Saif
Department of Medicine and Cancer Center; Tufts Medical Center; 800 Washington Street Box 245; Boston, MA 02111; USA
Phone: +1-617.636.5627; Fax: +1-617.636.8535
E-mail: wsaif@tuftsmedicalcenter.org

Data also lacks for differences in incidence of thromboembolism is various races and if race could be a factor predicting different outcomes in pancreatic cancer patients.

What We Learnt at the 2013 ASCO Gastro-intestinal Cancers Symposium?

Is There Any Potential Role of Anticoagulation in Pancreatic Cancer? (Abstract #284) [7]

Sigal *et al*. reported preliminary results as part of run in phase of randomized phase II trial [7]. Previously untreated 10 patients with metastatic pancreatic cancer were enrolled to receive 2-O, 3-O desulfated heparin 4 mg/kg bolus followed by a 48 h i.v. infusion at a dose of 0.375 mg/kg/h on days 1, 8, 15 and 28 until disease progression or unacceptable toxicity. The primary objective was progression free survival.
Median progression free survival was expected to exceed 6 months. 2-O, 3-O desulfated heparin was observed to be well tolerated by all patients without significant marrow toxicity and none of patients developed grade 3-4 thrombocytopenia or grade 4 neutropenia. It was concluded that patient benefit from 2-O, 3-O desulfated heparin in combination with gemcitabine and *nab*-paclitaxel.

Venous Thromboembolism in Asian Patients (Abstract #151) [8]

Lee *et al*. reported a retrospective study by reviewing medical charts of pancreatic cancer patients in order to determine the incidence of thromboembolism in East Asian patient population. They found 1,334 patients in their records but 1,116 met the inclusion criteria [8]. They used Cox proportional hazards model to analyze the association of pancreatic cancer and thrombo-embolism.
Their data showed an overall incidence of venous thromboembolism of 13.9% and 1-year cumulative thromboembolism incidence was 11.2%. The calculated incidence rate per 100 person-year at 6 months, 1-year, and 2-year was 23.4, 17.7 and 15.6 respectively. There were 155 thromboembolic events in total and their breakdown is shown in Table 1.
In this study significant predictors for venous thromboembolism in multivariate analysis were:

- advanced metastatic stage of cancer (HR=2.08) and
- chemotherapy and radiotherapy including concurrent chemoradiotherapy (HR=1.52).

Venous thromboembolism predicted risks for:

- 1-year mortality (HR=1.44) and
- overall mortality (HR=1.45).

Head and neck venous thromboembolism *vs*. non head and neck was associated with highest overall mortality (HR=2.05).
In conclusion they found venous thromboembolism among 13.9% of their East Asian patients with pancreatic cancer which is not too far from incidence in other ethnic groups. Occurrence of any venous thromboembolism but especially head and neck venous thromboembolism predicted poor prognosis.

Discussion

These studies highlight two important aspects of pancreatic cancer patient care, the need of newer and more effective treatment options for thromboembolism in patients with pancreatic cancer and especially in patients with advanced stage of cancer while on chemotherapy plus/minus radiotherapy. These data also highlight the associated poor prognosis. Chemo-therapeutic agents like gemcitabine have resulted in modest survival benefit in pancreatic cancer patients compared to 5-FU [9]. A phase III trial showed the superiority of FOLFIRINOX (5-FU, leucovorin, irinotecan and oxaliplatin) over gemcitabine alone [10]. Despite all these advances, prognosis of pancreatic cancer remains poor, most importantly due to the late stage at the time of initial diagnosis. 2-O, 3-O desulfated heparin has been reported to interfere with pancreatic cancer invasion, metastasis and help reduce chemotherapy resistance by inhibiting P and L selectins, heparanase and the HMGB1-RAGE axis [7]. If it is proven in further studies it has potential of becoming a good adjunctive agent to standard chemotherapy in pancreatic cancer patients. However, this warrants an evaluation in a big randomized clinical trial.
Lee's study touches an important aspect of cancer epidemiology and diversity, especially with respect to racial and geographical differences [8]. They reported incidence of venous thromboembolism in Asian patient population which has not been described in detail in previous studies. Medical literature is lacking in studies comparing the incidence of thromboembolism in different ethnicities and the impact on survival. In an earlier retrospective study by Oh *et al*. which included 75 patients, low venous thromboembolism incidence of 5.3% in Asian patients with pancreatic cancer was reported [11]. There is a need for more studies to see if ethnicity may be a factor in the incidence of thromboembolism and has a role in prognosis patients with in pancreatic cancer. Various studies have revealed modest survival benefit with the use of warfarin and low molecular weight heparin [12, 13]. The safely of anticoagulation has been shown in multiple studies. Nakchbandi *et al*. reported in a prospective and a retrospective study the safely of low dose warfarin in pancreatic cancer patients with favorable survival benefits [12]. Similarly safety of low molecular weight heparin has been reported in pancreatic cancer patients on chemotherapy [5, 13].

Table 1. Sites of thromboembolism in Asian patients.

Site	Incidence of thromboembolism
Abdominal venous thromboembolism	52.9%
Deep venous thrombosis	21.3%
- Pulmonary embolism	19.4%
- Head and neck venous thromboembolism	18.7%

Due to high incidence and associated poor prognosis there is an emergent need to define the use of anticoagulation in this high risk patient population.

Conflicts of interest The authors have no conflicts to disclose

References

1. Shaib, W., et al., Assessing risk and mortality of venous thromboembolism in pancreatic cancer patients. Anticancer Res, 2010. 30(10): p. 4261-4.

2. Sgouros, J. and A. Maraveyas, Excess premature (3-month) mortality in advanced pancreatic cancer could be related to fatal vascular thromboembolic events. A hypothesis based on a systematic review of phase III chemotherapy studies in advanced pancreatic cancer. Acta Oncol, 2008. 47(3): p. 337-46.

3. Chew, H.K., et al., Incidence of venous thromboembolism and its effect on survival among patients with common cancers. Arch Intern Med, 2006. 166(4): p. 458-64.

4. Al Diab, A.I., Cancer-related venous thromboembolism: insight into underestimated risk factors. Hematol Oncol Stem Cell Ther, 2010. 3(4): p. 191-5.

5. Burtness, B., et al., Phase II trial of weekly docetaxel/irinotecan combination in advanced pancreatic cancer. Cancer J, 2007. 13(4): p. 257-62.

6. Riess, H., et al., Rationale and design of PROSPECT-CONKO 004: a prospective, randomized trial of simultaneous pancreatic cancer treatment with enoxaparin and chemotherapy). BMC Cancer, 2008. 8: p. 361.

7. Sigal, D.M., GM. Rosen, SJ. Lee, P. Nguyen, T. Gribbin, TE. Diez, PQ. Borad, MJ. , Association of 2-O, 3-O desulfated heparin (ODSH) plus combination gemcitabine (G)/ nab-paclitaxel (A) with preliminary benefit in untreated metastatic pancreatic cancer. J Clin Oncol, 2013. 30(Suppl 34; Abst 284)).

8. Lee, J.C., J. Ro, YS. Hyejin, C. , Venous thrombo-emboembolism in patients with pancreatic cancer: Incidence and effect on survival in east Asian ethnic groups. J Clin Oncol, 2013. 30(Suppl 34; Abstr 151)).

9. Burris, H.A., 3rd, et al., Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol, 1997. 15(6): p. 2403-13.

10. Becouarn, Y., et al., A randomized phase II trial evaluating safety and efficacy of an experimental chemotherapy regimen (irinotecan + oxaliplatin, IRINOX) and two standard arms (LV5 FU2 + irinotecan or LV5 FU2 + oxaliplatin) in first-line metastatic colorectal cancer: a study of the Digestive Group of the Federation Nationale des Centres de Lutte Contre le Cancer. Ann Oncol, 2007. 18(12): p. 2000-5.

11. Oh, S.Y., et al., Venous thromboembolism in patients with pancreatic adenocarcinoma: lower incidence in Asian ethnicity. Thromb Res, 2008. 122(4): p. 485-90.

12. Nakchbandi, W., et al., Prospective study on warfarin and regional chemotherapy in patients with pancreatic carcinoma. J Gastrointestin Liver Dis, 2008. 17(3): p. 285-90.

13. Icli, F., et al., Low molecular weight heparin (LMWH) increases the efficacy of cisplatinum plus gemcitabine combination in advanced pancreatic cancer. J Surg Oncol, 2007. 95(6): p. 507-12.