Review Article

Saddle Pulmonary Embolism in a Cancer Patient with Thrombocytopenia: A Treatment Dilemma

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The association between cancer and venous thromboembolism (VTE) is well established. Saddle pulmonary embolism is not uncommon in hospitalized cancer patients and confers a higher mortality. We report a case of saddle pulmonary embolism in a cancer patient with thrombocytopenia, discuss the bleeding risks, complexity of managing such patients and review current guidelines.

1. Introduction

Pulmonary embolism (PE) is common in hospitalized patients. Overall mortality for major pulmonary embolism is 22% and as high as 65% in those who require cardiopulmonary resuscitation [1]. Saddle pulmonary embolism in cancer patients carries a very poor prognosis, with mortality of >80% at one year [2]. A number of patients with cancer and pulmonary embolism have concomitant thrombocytopenia, posing a great therapeutic challenge.

We report a case of saddle pulmonary embolism in a cancer patient with thrombocytopenia and discuss the bleeding risks, complexity of managing such patients and review current guidelines.

2. Case Report

A 73-year-old female with history of hepatocellular carcinoma due to long-standing hepatitis C, presented to the emergency center with a sudden syncopal episode at home. Her past medical history was significant for portal hypertension, and variceal bleeding requiring blood transfusions. She was receiving sorafenib, which required dose reduction due to thrombocytopenia. Her platelets fluctuated between 46,000–113 × 10⁹ during the treatment.

On examination she was stable with a blood pressure of 128/72 mmHg; heart rate of 80 beats per minute; respiratory rate of 22/minute; temperature 36.7°C; and O₂ saturation of 96% on 2-3 liters oxygen via nasal cannula. Heart sounds were normal with no signs of heart failure.
In patients with PE, comorbidities like older age (>70 years), congestive heart failure, RV dysfunction and cancer increase the likelihood of mortality by at least 2–3-fold [3].

Cancer induces a prothrombotic state [5, 6]. Malignant neoplasm alone is associated with a 4-fold increased risk of VTE without chemotherapy, and cytotoxic immunosuppressive therapy increases the risk to more than 6-fold [7]. The most common chemotherapy agents associated with VTE are: thalidomide, lenalidomide with or without dexamethasone, L-asparaginase, bevacizumab, tamoxifen, estramustine, cepacitanib, erlotinib, sunitinib, vinorelbine, trastuzumab, paclitaxel-albumin-bound, letrozole, and bortezomib [8]. In addition to chemotherapy agents, central venous catheters (CVC) also act as predisposing factors. The incidence of venographic CVC-related DVT in cancer patients varies from 27% to 66% [9]. Risk of VTE also increases significantly in patients undergoing major surgical procedures for cancer [10].

Saddle pulmonary embolism in cancer patients carries a very poor prognosis, with mortality of >80% at one year [2]. The treatment of saddle pulmonary embolism, particularly in the setting of concomitant thrombocytopenia, remains unclear and creates a great therapeutic challenge. The issue of treating thrombotic disease in cancer patients with thrombocytopenia secondary to myelosuppressive therapy has not been studied in large randomized clinical trials and therapy in these cases should be individualized based on risk benefit ratio.

3. Discussion

Venous thromboembolism (VTE) is common in cancer patients; with significant in hospital mortality [1, 3]. In a large retrospective cohort study of hospitalized cancer patients, overall incidence of VTE was 4.1% [4]. Cancer patients with VTE have higher in-hospital mortality compared to those who did not have VTE (16.3% versus 6.3%; \( P < .001 \)) [4]. In patients with PE, comorbidities like older age (>70 years), congestive heart failure, RV dysfunction and cancer increase the likelihood of mortality by at least 2–3-fold [3].

In another randomized trial of 676 cancer patients with VTE in which dalteparin in a dose adjusted protocol (200 IU/Kg daily for the first month and then 150 IU/Kg daily for the next 5 months) was compared to warfarin, there was...
a significant decrease in the cumulative risk of recurrent VTE in patients receiving dalteparin compared to warfarin (8.3% versus 13.8%; hazard ratio, 0.48; \( P = .002 \)). PE with or without DVT comprised only 30% of total enrolled patients [17].

In another trial of 91 cancer patients with VTE, in which 3 different regimens were compared: (1) enoxaparin 1.0 mg/Kg twice daily for 5 days followed by once daily 1.0 mg/Kg for 175 days; (2) enoxaparin 1.0 mg/Kg twice daily for 5 days then enoxaparin 1.5 mg/Kg once daily for 175 days; (3) enoxaparin 1.0 mg/Kg twice daily with warfarin for minimum of 5 days with an INR goal of 2–3; there were no significant differences between enoxaparin and warfarin in safety profile and recurrent VTE. In this study 45% of cancer patient with VTE had PE [18].

In a recent study of 200 cancer patients with VTE, in which tinzaparin in a dose of 175 International Factor Xa Inhibitory Units/Kg was compared to warfarin for an INR goal of 2–3, there was a significant decrease in cumulative risk of recurrent VTE at 10 months in patients assigned to tinzaparin (\( P = .044 \)) [19]. In this trial, only 21% of patient had PE [19]. A recent meta-analysis showed superiority of LMWH over VKA in lowering rates of recurrent VTE in cancer patients [20]. Low-molecular-weight heparins (LMWHs) have become anticoagulants of choice due to their predictable pharmacokinetic and pharmacodynamic profiles. These agents are not therapeutically interchangeable due to their different molecular weight, half-life, and antiXa to IIa ratio [21]. LMWHs are considered intermediate acting anticoagulants with predictable kinetics. Specific pharmacokinetics of different anticoagulants, platelet monitoring, and recommendation for reversal in cases of bleeding are reviewed in Table 2. Monitoring of antiXa is recommended in obese patients, underweight patients, and patients with renal insufficiency, due to accumulation of LMWHs [22–27].

Warfarin is considered an alternative agent to LMWH. Due to major drug interactions between warfarin and chemotherapy, nutritional deficiency, and use of nonchemotherapy agents in cancer patients, frequent dose monitoring and modifications for warfarin is needed.

The difficulty in maintaining the narrow therapeutic index of warfarin also was shown in a major cancer trial where a therapeutic range INR (2-3) was achieved in only 46% of the patients [17]. Risk of VTE recurrence increases with subtherapeutic INR [30].

Direct factor-Xa inhibitor, fondaparinux, can also be considered for the initial (acute phase) treatment of PE. Fondaparinux was studied in a randomized clinical trial that showed noninferiority to unfractionated heparin in the acute treatment of PE; however, only 20% of patients enrolled in each arm had cancer. The incidence of VTE recurrence was 3.8% in the fondaparinux group and 2.4% in the unfractionated-heparin group, for an absolute difference in favor of fondaparinux of 1.2% (95% confidence interval, \(-3.0 \text{ to } 0.5\)). The reported incidence of major bleeding was 2% in the fondaparinux group and 2.4% in the unfractionated-heparin [33]. Due to lack of extended treatment trials, the role of fondaparinux for long-term treatment of VTE in cancer patients is unknown [13–15, 28].

Recently fixed-dose subcutaneous weight-adjusted unfractionated heparin (UFH) has also been recommended for the acute treatment of VTE [15]. The strength of this recommendation is weak and is based only on 2 studies,
Table 2: Pharmacokinetics of different anticoagulants [22–29].

| Anticoagulant       | Molecular weight | T1/2 (h) | Elimination route | Antidote | Platelet monitoring | AntiXa monitoring |
|---------------------|------------------|----------|-------------------|----------|---------------------|-------------------|
| Enoxaparin (lovenox) | 3,500–5,500      | 4.5–7    | Renal             |          |                     | - 1 mg/kg         |
|                     |                  |          |                   | Protamine sulfate 1 mg per 100 U of heparin or less than 100 mg over 2 hours to lower risk of reaction. Protamine partially reverses the effect of LMWH | Q12 = 0.6–1.1 IU/mL | - 1.5 mg/kg daily = 1.0–1.5 IU/mL |
| Dalteparin (fragmin)| 5,600–6,400      | 3–5      | Renal             |          |                     | - 100 IU/kg       |
|                     |                  |          |                   | Protamine sulfate 1 mg per 100 U of heparin or less than 100 mg over 2 hours to lower risk of reaction. Protamine partially reverses the effect of LMWH | Q12 = 0.4–1.1 IU/mL | - 200 IU/kg daily = 1.0–2.0 IU/mL |
| Tinzaparin (innohep)| 5,600–7,500      | 3–4      | Renal             |          |                     | 175 IU/kg = 0.85–1.0 IU/mL |
|                     |                  |          |                   | Protamine sulfate 1 mg per 100 U of heparin or less than 100 mg over 2 hours to lower risk of reaction. Protamine partially reverses the effect of LMWH | aPTT monitoring | - Thrombocytopenia of any degree should be monitored |
| Unfractionated heparin | 5,000–30,000   | 1–2      | Renal/endothelial |          |                     | - Discontinue for platelet count below 100,000/mm³ |
|                     |                  |          |                   | Protamine sulfate 1 mg per 100 U of heparin or less than 100 mg over 2 hours to lower risk of reaction. Protamine partially reverses the effect of LMWH | aPTT monitoring | - 2.5 mg = peak at steady state 0.39–0.5 mg/L; trough at steady state 0.14–0.19 mg/L |
| Fondaparinux (arixtra) | <2,500           | 17–21    | Renal             |          |                     | - 5 mg, 7.5 mg, 10 mg = peak at steady state 1.20–1.26 mg/L; trough at steady state 0.46–0.62 mg/L |

IV: intravenous; SC: subcutaneous; U: unit; UFH: unfractionated heparin; LMWH: low-molecular-weight heparin; T1/2: half-life elimination; HIT: heparin-induced thrombocytopenia; aPTT: activated partial thromboplastin time.

Each including only 22% patients with cancer with less than 20% patients with PE. Patients with hemodynamic compromise were excluded from these trials; therefore, PE patients with cardiovascular compromise should not receive UFH subcutaneously [15].

Recommended treatment duration of VTE in cancer patients is 6–12 months and indefinite in cases of metastatic or active cancer [11–15].

3.3. Thrombolytics. In the absence of contraindications, systemic thrombolytics should be considered in patients with massive PE and hemodynamic instability [11, 15]. The recommended dose of r-tPA is 100 mg intravenously over 2 hours via peripheral vein [15].

However, cancer patients have been excluded from thrombolytic trials; hence evidence-based guidelines for the use of thrombolytics in this subset of population is lacking.

Except for a case report where streptokinase was used for the treatment of PE associated with heparin-induced thrombocytopenia [35], no other data exists on the use of thrombolytics in patients with PE and thrombocytopenia. Clinical judgment should be used and therapy individualized in each case.

3.4. Thrombectomy. Catheter and surgical thrombectomy are an option in selected patients. In a pregnant patient with PE and thrombocytopenia (due to myelodysplastic syndrome), successful emergency pulmonary embolectomy has been reported [36]. However, large-scale data in cancer patients is lacking [15].

3.5. IVC filter. Placement of IVC filter is recommended in patients with contraindication to anticoagulation, failure of
anticoagulation, massive pulmonary embolism, severe cardiopulmonary disease with deep vein thrombosis, and free floating iliofemoral or inferior vena cava thrombus [11–15, 37]. To date, there are no randomized clinical trials available in the cancer literature to assess the long-term safety and efficacy of filters. IVC filters carry short-term and long-term complications such as hematomas; misplacement, migration, thrombosis, recurrent PE, filter fracture, IVC occlusion and vena caval syndrome [38]. The insertion of an IVC filter does not obviate the need for long-term anticoagulation [15].

3.6. Assessing and Addressing Bleeding Risks. Prior to initiation of anticoagulation risk of bleeding should be assessed. Reported bleedings (major and minor combined) in cancer trials associated with VKA and LMWH are 3%–16% and 6%–11%, respectively [8, 23]. The Prospective registry, Registro Informatizado de La Enfermedad Thromboembólica (RIETE), showed that patients with VTE and evidence of recent major bleed (<30 days prior to diagnosis of VTE) had significantly higher rates of fatal bleeding (4.1% versus 0.6%; \(P < .001\)) and mortality (9.5% versus 7.7%; \(P < .005\)) compared to those without [39]. Multivariate analyses of RIETE showed that patients with a body weight of less than 60 kilograms, serum creatinine of >1.2 mg/dL, recent major bleeding, immobility for >4 days, clinically overt PE, and metastatic cancer had higher odds of developing fatal or major bleeding (Table 3) [31, 32]. When RIETE investigators cross-validated the predictive model into a validated group, after determination of point scores, the incidence of major bleeding was 0.1% (95% CI: 0.0–0.2) in low-risk patients; 2.8% (95% CI: 2.4–3.3) in those at intermediate risk, and 6.2% (95% CI: 4.0–9.1) in high-risk patients. The incidence of major bleeding in the three groups was statistically different (\(P < .001\)) (Table 4) [34]. These prospective data have not measured the effect of thrombocytopenia into the bleeding risk scores. Advanced age, renal insufficiency, metastatic cancer, anemia, immobility, recent major bleeding, and clinically overt PE should prompt healthcare providers to closely monitor these patients for bleeding complications while receiving anticoagulation.

Transient thrombocytopenia due to myelosuppressive chemotherapy needs to be taken into consideration prior to initiation of anticoagulation as bleeding risks double from 10% at a platelet count of 20,000/mm³ to 20% when the platelet count drops to below 10,000/mm³ in solid tumor patients [40]. The timing and kinetics of platelet nadir is dependent on the mode of action, dose, and addition of multiple cytotoxic agents. Cytotoxic agents such as ifosfamide, carboplatin, etoposide, mesna, doxorubicin, and dacarbazine are associated with an early nadir. Delayed nadir can be seen in regimens containing nitrosoureas and melphalan. Novel agents such as lenalidomide and bortezomib can contribute to thrombocytopenia when added to other cytotoxic agents [40]. Enrolling cancer patients in VTE trials has been limited due to strict inclusion criteria; mainly to prevent bleeding complications. Cancer trials for VTE have excluded patients with platelet count as low as 30,000/mm³ to as high as 150,000/mm³ [16–19]. National Comprehensive Cancer Network (NCCN) considers platelet counts of less than 50,000/mm³ as a contraindication to prophylactic or therapeutic anticoagulation therapy [14]. American Society of Clinical Oncology (ASCO) recommends using therapeutic

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### Table 3: Multivariate analysis of the risk of developing fatal and major bleeding in cancer patients with venous thromboembolism (VTE) [31, 32].

| Variables                        | Odds ratio (95% CI) | \(P\)-value | Variables                        | Odds ratio (95% CI) | \(P\)-value |
|----------------------------------|--------------------|-------------|----------------------------------|--------------------|-------------|
| Body weight <60 kg               | 2.5 (1.1–5.3)      | .021        | Recent major bleeding            | 2.4 (1.1–5.1)      | .003        |
| Recent major bleeding            | 3.0 (0.96–9.1)     | .058        | CrCl < 30 ml/min                 | 2.2 (1.5–3.4)      | <.001       |
| Serum creatinine >1.2 mg/dL      | 2.8 (1.3–5.8)      | .008        | Immobility for ≥4 days           | 1.8 (1.2–2.7)      | .005        |
| Immobility for ≥4 days           | 4.1 (1.9–8.7)      | .001        | Metastatic cancer                | 1.6 (1.1–2.3)      | .03         |
| Metastatic cancer                | 3.1 (1.4–7.1)      | .006        |                                  |                    |             |

Confidence interval: CI; creatinine clearance: CrCl.

### Table 4: Multivariate analysis for major bleeding and bleeding risk index classification [34].

| Risk factors                                   | Odds ratio (95%CI) | \(P\) | Points |
|------------------------------------------------|--------------------|--------|--------|
| Recent major bleed                             | 2.7 (1.6–4.6)      | <.001  | 2      |
| Serum creatinine >1.2 mg/dL                    | 2.1 (1.7–2.8)      | <.001  | 1.5    |
| Anemia                                         | 2.1 (1.7–2.7)      | <.001  | 1.5    |
| Cancer                                         | 1.7 (1.4–2.2)      | <.001  | 1      |
| Clinically overt pulmonary embolism            | 1.7 (1.4–2.2)      | <.001  | 1      |
| Age >75 y                                      | 1.7 (1.3–2.1)      | <.001  | 1      |

0 point: low risk 0.1% (95% CI: 0.0–0.2) 1–4 points: intermediate risk 2.8% (95% CI: 2.4–3.3) >4 points: high risk7.3 % (95% CI: 4.0–9.1)
anticoagulation in cancer patients with preexisting thrombocytopenia with caution; therefore, close monitoring of platelets and hemoglobin is required in cancer patients [13]. Choosing an anticoagulant should be based upon the half-life, reversibility, tolerability, patient’s preference, and cost [13]. Pharmacokinetic, pharmacodynamic, and monitoring parameters specific to each anticoagulant are discussed in Table 2. Briefly, unfractionated heparin provides a short half-life with complete reversibility by protamine sulfate; therefore, it is considered ideal agent for patients that may require rapid surgical interventions such as thrombectomy. LMWHs are considered intermediate to long-acting agents. Partial reversal of LMWHs in bleeding can be achieved by use of protamine sulfate. The half-life of fondaparinux is longer than LMWHs and partial reversibility can be achieved by administration of Recombinant factor VIIa (rVIIa) in bleeding episodes [15, 23]. Vitamin K can be administered for reversal of bleeding associated with VKA. Fresh frozen plasma and cryoprecipitate can be administered in cases of life-threatening bleeding associated with anticoagulants [15]. In patients taking warfarin, Food and Drug Administration (FDA) has made recommendations regarding the potential benefits of genotype testing, to help reduce the bleeding risks in individual patients. Risk of intracranial hemorrhage with thrombolytics in PE is about 3% [3]. In a study of 104 patients with acute PE who received fibrinolytic therapy, 19% of patients experienced major bleeding. In this study, cancer, diabetes, and an elevated INR before initiation of fibrinolytic therapy were found to be an independent predictors of major bleeding [41].

The exact risk of bleeding in thrombocytopenic patients with PE is unknown. Platelet count less than 150,000/mm³ has been a predictor of short-term composite event such as mortality [42]. In clinical practice, platelet count of less than 50,000 × 10⁹ is a contraindication to thrombolytic therapy [43].

No recommendations can be made regarding the use of thrombolytics in patients with thrombocytopenia and acute PE, until large-scale data is available. Use of thrombolytic agents in cancer patients requires close attention to bleeding risks and overall prognosis.

4. Conclusion

There are several published guidelines for the treatment of VTE in cancer patients.

However, data on the management of saddle PE and particularly in patients with thrombocytopenia is lacking. Large-scale prospectively collected data and future studies are needed to address the best possible treatment option in these patients.

Conflict of Interests

The authors do not report any conflict of interests regarding this work.

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