Impact of Pharmacists’ Interventions on Prescribing Patterns for the Treatment of VTE in Patients with Cancer

Vikki M. Steward, PharmD; Hind Hamid, PharmD; Kimberly Hooker, PharmD

Background: Venous thromboembolism (VTE) is a common comorbidity and a significant complication among patients with cancer. Its management can be quite problematic for medical oncologists. Guidelines recommend low-molecular-weight heparin (LMWH) monotherapy for 6 months as the preferred treatment, and it is important for the prescribing patterns of medical oncologists to align with these recommendations to ensure optimal patient care.

Objectives: The main objectives of this study were to assess the medical oncologists’ prescribing patterns for VTE treatment among patients with cancer at DCH Regional Medical Center, to make clinical interventions in an effort to comply with the guideline recommendations, and to assess the impact of these clinical interventions.

Methods: A retrospective chart review of patients with cancer who were diagnosed with VTE between January 2010 and June 2010 was conducted to assess their prescribed treatment regimens. Pharmacists made clinical interventions consisting of education to healthcare providers, development of VTE treatment preprinted order forms, and direct recommendations to align prescribing patterns with the preferred guidelines’ recommendation. Thereafter, prospective data of medical oncologists’ prescribing patterns were collected during three 5-week segments (15 weeks).

Results: Thirty-nine of the 54 patients with cancer in the retrospective chart review met the inclusion criteria. Three (8%) patients were prescribed LMWH monotherapy for the treatment of VTE. After pharmacists’ educational interventions and collaboration with medical oncologists, 70% of patients who were assessed were prescribed LMWH monotherapy (P = .001) in accordance with the guidelines’ recommendation for VTE treatment. This desired prescribing pattern decreased to 59% in the absence of a pharmacist’s collaboration. Nevertheless, a significant difference (P < .05) was found for the prescribing of LMWH monotherapy by medical oncologists after pharmacists’ interventions compared with the initial review of such prescribing patterns.

Conclusion: This study shows that although initially sporadically prescribed, LMWH monotherapy for VTE treatment in patients with cancer significantly increases after interventions by pharmacists.
obesity, pulmonary, renal, and/or cardiac disease, are at increased risk for VTE. Chemotherapy or hormone therapy and indwelling central venous catheters, which are often used in the medical oncology setting, also present as clinical risk factors for developing VTE. Chemotherapy increases the risk of VTE and recurrent VTE by 6-fold and 2-fold, respectively. Specifically, the agents thalidomide and lenalidomide, which are frequently used for the treatment of multiple myeloma and myelodysplastic syndrome, are strongly associated with the risk of VTE. For patients receiving these agents, prophylactic anticoagulation is typically initiated to lower the incidence of VTE.

Although the pathophysiology of thrombosis formation and blood coagulation in patients with cancer has been studied for many years, it remains poorly understood. Research suggests that the cause of thrombosis is associated with malignant cells that are potentially secreting procoagulants (cysteine protease that directly activates factor X) and are stimulating the immune system to secrete cytokines that increase coagulopathy. Endothelial cell injury and inflammation associated with malignancy can result in coagulation activation and elevated clotting factors. This may explain why patients with cancer exhibit a high rate of resistance to the oral anticoagulant warfarin. In addition, solid tumors compressing vessels can cause turbulent blood flow, which increases the risk of coagulation.

The standard regimen for VTE treatment among the general medically ill patient population typically consists of unfractionated heparin, fondaparinux, or low-molecular-weight heparin (LMWH) for the initial 5 to 10 days, overlapping with warfarin to bridge to subsequent extended anticoagulant therapy (≥3 months). This regimen has been shown to be effective for most patients pending appropriate compliance to therapy. Therefore, it is logical to think of this approach as an appropriate option for a patient with cancer who is presenting with VTE. However, in the recently published American College of Chest Physicians (ACCP) Guidelines (9th edition), the ACCP suggests the use of LMWH extended anticoagulant therapy over vitamin K antagonist therapy as the preferred treatment of VTE in patients with cancer.

LMWHs are favored over other treatment options, because they can conveniently be administered in an outpatient setting and are associated with a reduced risk of developing adverse effects, such as heparin-induced thrombocytopenia. Publication of the Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) trial demonstrated evidence for LMWH superiority over warfarin without increasing the risk of bleeding.

Patients with cancer exhibit a high rate of resistance to warfarin, and there are other significant issues associated with the use of warfarin to treat patients with cancer. Variability in dietary intake, potential liver dysfunction, and chemotherapy-induced nausea and vomiting make it difficult to achieve the target international normalized ratio (INR) of 2.0 to 3.0. Anticoagulation with warfarin can also be hazardous because the chemotherapy regimens, as well as the supportive therapy, are more likely to have drug interactions with oral anticoagulants, thereby altering the dose requirement. Therefore, warfarin therapy requires more frequent monitoring than the guidelines’ recommended LMWH monotherapy. Invasive surgical procedures, concomitant radiation therapy, and metastases, particularly those to the brain, often lead to interruption in oral anticoagulation to avoid supratherapeutic INRs and potential hemorrhage. This interruption in oral anticoagulation therapy can, in turn, place the patient at significant risk for recurrent thrombosis.

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Despite the known issues regarding VTE management in patients with cancer, we hypothesized that the prescribing patterns of the medical oncologists at DCH Regional Medical Center (RMC) do not correspond with preferred treatment guidelines for VTE, but instead mimic treatment options for acute VTE among the medically ill patient population. This study evaluated prescribing practices, while allowing the principal investigator the opportunity to make patient-specific recommendations and to provide education for all healthcare providers involved in the care of patients with cancer.

Methods
This research was a single-center study conducted at DCH RMC, which is located in Tuscaloosa, AL, and is a community owned, not-for-profit hospital licensed for approximately 600 beds. It is the flagship hospital within the DCH Health System and a major referral center, serving 11 western Alabama counties. Oncology is an area of specialty provided at DCH Cancer Center, a hospital-based cancer center affiliated with M.D. Anderson Physicians Network. The research was approved by the DCH Health System Institutional Review Committee in December 2010. Throughout all parts of the study, 4 medical oncologists were staffed at the institution. The
principal investigator was a postgraduate year 1 pharmacy practice resident.

**Part 1**

Part 1 of the study was a retrospective chart review. Diagnosis-related group (DRG) codes were used to identify all patients with cancer between January 2010 and June 2010 who had a primary or secondary documented diagnosis of VTE. The documented VTE could be either a deep-vein thrombosis (DVT; DRG code 453.4) and/or a pulmonary embolism (PE; DRG code 415.19). Patients were excluded if they met any of the following criteria: age ≥18 years; diagnosis of benign tumors; diagnosis of myeloproliferative disorders, multiple myeloma, or myelodysplastic syndrome, as well as any other diagnosis for which thalidomide or lenalidomide was included within the chemotherapy regimen; and laboratory work performed at a facility other than DCH RMC. Data collection included patient demographics, cancer type, documented date of VTE event(s), number of VTE events during part 1 of the study, prescribed VTE treatment regimen, length of LMWH therapy (if available), and details regarding warfarin therapy if used within the VTE treatment regimen.

The primary objective of part 1 was to assess whether the prescribing patterns of the medical oncologists corresponded with the preferred guidelines for the treatment of VTE in patients with cancer. At the time the study was conducted, the preferred guidelines referred to the most current guidelines published by the American Society of Clinical Oncology, the ACCP, and the National Comprehensive Cancer Network, all of which recommend the use of LMWH monotherapy for 6 months. Concomitant use of warfarin within the majority of VTE treatment regimens was anticipated. Therefore, the secondary objective was to evaluate the frequency of optimal INRs among the physician-managed oral anticoagulation therapy. INR collection began 5 to 7 days after initiation of warfarin therapy or once the INR was ≥2.0, and all subsequent INRs were collected for 6 months. The INRs were reviewed and classified as therapeutic (target range, 2.0-3.0) or nontherapeutic (<2.0 or >3.0). Patients receiving thalidomide or lenalidomide as a part of their chemotherapy regimen were excluded, because they were likely receiving prophylactic anticoagulation.

**Parts 2 and 3**

In parts 2 and 3 of the study, the principal investigator made clinical recommendations for LMWH monotherapy in an effort to establish the evidence-based guidelines’ recommendation as the standard of care at the institution. Specifically, in part 2, both inpatient and outpatient oncology VTE treatment preprinted order forms were developed and approved by the medical oncologists and the DCH Forms Committee. Each form included an indication for LMWH use, dosing information (including dosage adjustments), duration of therapy, monitoring parameters, orders for patient self-administration education, orders for case management and/or medication assistance involvement, and scheduled follow-up visits. The primary objective of part 2 was to help make prescribing LMWH monotherapy more convenient for medical oncologists.

Part 3 of the study consisted of the principal investigator providing an educational series of presentations and newsletter articles to all healthcare providers involved in the care of patients with cancer. The medical oncologists were presented with the results of the part 1 retrospective chart review revealing their prescribing patterns and a detailed explanation of the evidence-based literature supporting the preferred recommendation for the treatment of VTE in patients with cancer. The pharmacy and nursing staffs were presented with an overview of VTE among patients with cancer, the preferred treatment recommendation and suggestions on how to identify patients at risk and how to intervene to optimize patient care, and, finally, they were introduced to the inpatient and outpatient VTE treatment preprinted order forms.

Pharmacists were instructed to determine whether orders and prescriptions for LMWH were for treatment or for prophylaxis therapy, and to make clinical interventions to ensure optimal dosing and use of the preprinted order forms when appropriate. Furthermore, education involved composing an article for Chemo Savvy, the newsletter for DCH Cancer Center Physicians, as well as another article for P&T News, the hospital’s Pharmacy and Therapeutics Committee newsletter. The primary objective of part 3 was to increase the multidisciplinary team’s awareness of the evidence-based guideline recommendation for VTE treatment among patients with cancer.

**Part 4**

The final part of the study, part 4, was a 15-week prospective period divided into three 5-week segments. The initial 5-week segment consisted of an evaluation of the medical oncologists’ prescribing patterns for the post-educational intervention-only period. During this segment, any patient with cancer and suspected VTE was reported to the principal investigator by the oncology nursing staff. The principal investigator would then follow the patient to confirm the VTE diagnosis and to collect the treatment regimen that was prescribed by the medical oncologist. Pharmacists did not engage in any collaborative efforts with medical oncologists during this segment.

During the second 5-week segment of part 4, the principal investigator screened and followed patients with
cancer concurrently with the 4 medical oncologists. If an acute VTE was documented, the principal investigator collaborated with the patient’s medical oncologist regarding the patient and made a direct recommendation for the guidelines’ preferred treatment, LMWH monotherapy, as appropriate.

After the second 5-week segment, there was a 3-week dormant period during which the principal investigator discontinued concurrent interventions and collaboration with the medical oncologists.

Thereafter began the third and final 5-week segment of part 4. This segment was similar to the second 5-week segment; however, the principal investigator did not discuss the patients with the medical oncologists if an acute VTE was documented and did not intervene regarding their prescribing patterns. In turn, the medical oncologists did not consult the principal investigator for VTE treatment recommendations. Instead, the principal investigator observed and recorded the medical oncologists’ prescribing patterns. The primary objective of part 4 was to evaluate the impact of the previous clinical interventions. Data collected for each patient in part 4 were the same as previously defined for the retrospective chart review in part 1 of the study.

All data were collected and interpreted by the principal investigator. The hospital statistician and the principal investigator analyzed the data. Statistical analysis using Pearson’s chi-squared test was performed for non-parametric data to evaluate the impact of the clinical interventions. The P value of significance was .05.

**Results**

**Part 1**

A total of 75 patients were identified through the hospital database search for having a diagnosis of cancer, as well as a diagnosis of VTE, between January 2010 and June 2010. Of these, 54 patients met the inclusion crite-
ria for the retrospective chart review. During the retrospective chart review, it was discovered that 15 of these patients met the exclusion criteria. Therefore, the study population for part 1 consisted of 39 patients (Figure 1).

Patients within the part 1 study population were predominantly male (62%) and aged 22 to 89 years (mean, 66 years). This population consisted of a variety of cancer types. The 2 types representing the majority of patients were lung (31%) and prostate (26%) cancer. PE was the most prevalent (49%) type of VTE event among the part 1 study population; however, 18% of the patients were diagnosed with a DVT and a PE during the study period. Six patients (15%) experienced a recurrent VTE event during the study period, 5 of whom had the same type of VTE event as before. The characteristics of the part 1 study population are shown in Table 1.

A total of 7 treatment regimens were prescribed by the medical oncologists when managing VTE in the observed patients with cancer, including: (1) heparin only; (2) heparin plus warfarin; (3) heparin plus LMWH; (4) heparin, LMWH, and warfarin; (5) LMWH only; (6) LMWH plus warfarin; and (7) inferior vena cava filter only. The LMWH-only treatment regimen represents the guidelines’ preferred recommendation of LMWH monotherapy. Of the 39 patients, 3 (8%) were prescribed the guidelines’ preferred recommendation of LMWH monotherapy. The majority (41%) of the part 1 study population received LMWH with concomitant warfarin to bridge into long-term anticoagulation therapy (Figure 2).

The vast majority (74%) of patients in part 1 were prescribed a VTE treatment regimen that involved warfarin as a component of their anticoagulation therapy. INRs were collected for the 6 months immediately after the documented VTE event for those patients, to assess whether they were being maintained within the therapeutic range of 2.0 to 3.0 for appropriate anticoagulation. The number of INRs collected per patient was inconsistent; however, more than 50% of the INRs were nontherapeutic for the heparin plus warfarin treatment regimen, and more than 65% were nontherapeutic for the remaining regimens (Figure 3). Of the nontherapeutic INRs, 69% of those obtained were subtherapeutic (INR <2.0), and the highest INR level obtained was 14.8.

Parts 2 and 3

The VTE inpatient and outpatient oncology treatment preprinted order forms were approved and implemented in February 2011. The educational presentation series was conducted by the principal investigator in January and February 2011, and it consisted of 7 total presentations to the medical oncologists, pharmacists, and nursing staff. Of the 4 medical oncologists, 3 attended at least 1 of the educational presentations. The inpatient pharmacists, cancer center pharmacists, and nursing staff each had 2 opportunities to attend an educational presentation. Approximately 20 pharmacists and 30 nurses attended the educational presentation. In addition, the educational newsletter articles were published in the February 2011 issue of Chemo Savvy and in the February/March 2011 issue of P&T News.
Part 4

The impact of the pharmacists’ interventions was assessed throughout the 15 weeks of part 4 of the study, which was divided into three 5-week segments. The first 5-week segment consisted of the evaluation of the medical oncologists’ prescribing patterns for the post-educational intervention-only period. Of the 12 patients with cancer who were reported to the principal investigator by the oncology nursing staff, 7 patients were screened for VTE, all of whom had a documented VTE (Table 2). Of these patients, 5 (71%) were prescribed the LMWH-only treatment regimen. Compared with the retrospective chart review in part 1, a significant difference ($P = .001$) was found among medical oncologists’ prescribing of LMWH monotherapy.

Data collected from the second 5-week segment involved direct collaboration with the medical oncologists regarding patient care. A total of 214 patients were screened on the inpatient and the outpatient medical oncology services. Among these 214 patients, 54 patients had a cancer diagnosis, 11 of whom were identified as having had a VTE event (Table 2). Of 11 documented VTE events, 8 (73%) were treated with the LMWH-only regimen, which again was significant ($P = .001$) compared with part 1 of the study. Only 1 patient from the initial 5-week segment and 1 patient from the second 5-week segment (14% and 9%, respectively) received therapy with LMWH plus warfarin, which was the most prevalent treatment regimen in part 1.

A 3-week dormant period was allowed before the beginning of the third 5-week segment of part 4 to transition to independent prescribing of VTE treatment by the medical oncologists. In the final 5-week segment, 217 patients were screened on the oncology service and 68 of them were actual patients with cancer. Of

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Part 4 Patient Population for Each 5-Week Segment</th>
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<tr>
<td></td>
<td>First 5-week segment</td>
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<tr>
<td>Total patients identified, N</td>
<td>12</td>
</tr>
<tr>
<td>Excluded patients, N</td>
<td>2</td>
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<tr>
<td>Total patients with cancer, N</td>
<td>10</td>
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<tr>
<td>Total patients with cancer screened for VTE, N</td>
<td>7</td>
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<tr>
<td>Total documented VTEs, N</td>
<td>7</td>
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VTE indicates venous thromboembolism.

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<thead>
<tr>
<th>Table 3</th>
<th>Summary of Prescribing Patterns for VTE in Patients with Cancer</th>
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<tr>
<td>Treatment regimens</td>
<td>Part 1 results, retrospective</td>
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<tr>
<td></td>
<td>Before pharmacist’s intervention (N = 39)</td>
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<tr>
<td>Heparin only, N (%)</td>
<td>3 (8)</td>
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<tr>
<td>Heparin plus warfarin, N (%)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Heparin plus LMWH, N (%)</td>
<td>1 (2)</td>
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<tr>
<td>Heparin, LMWH, plus warfarin, N (%)</td>
<td>5 (13)</td>
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<tr>
<td>LMWH only$^b$, N (%)</td>
<td>3 (8)</td>
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<tr>
<td></td>
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</tr>
<tr>
<td>LMWH plus warfarin, N (%)</td>
<td>16 (41)</td>
</tr>
<tr>
<td>IVC filter only, N (%)</td>
<td>3 (8)</td>
</tr>
</tbody>
</table>

$P < .05$.

$^a$Period between educational presentations to medical oncologist’s and pharmacist’s concurrent intervention.

$^b$Significant difference between prescribing LMWH only in part 1 and in all components of part 4.

IVC indicates inferior vena cava; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.
the patients with cancer, 14 were found to have had a documented VTE event (Table 2), 6 (43%) of whom had VTE events that were treated with LMWH only. Although still significant, this percentage of LMWH monotherapy treatment regimens prescribed is slightly decreased from when there was a pharmacist’s collaboration. A summary of the results of parts 1 and 4 of the study are outlined in Table 3.

Discussion

This study demonstrates that the medical oncologists at DCH RMC are receptive to pharmacists’ interventions to comply with evidence-based guidelines in the form of education and patient-specific recommendations. This statement is supported by the statistical significance found in the increased prescribing of the guidelines’ preferred recommendation, LMWH monotherapy, after pharmacists’ interventions compared with previous prescribing patterns (from 8% to 73%). This is important, because patients with cancer are at an increased risk for developing VTE and recurrent VTE. Therefore, medical oncologists should be aware of this evidence to optimize patient care.

This study demonstrates that the medical oncologists at DCH RMC are receptive to pharmacists’ interventions to comply with evidence-based guidelines in the form of education and patient-specific recommendations.

There are several strengths to our study. First, the study has used evidence-based recommendations to optimize patient care. Studies have already demonstrated the effectiveness of 6-month LMWH monotherapy in patients with cancer; this is the rationale supporting the acceptance of this recommendation, which is in accordance with current guidelines.

Second, the assessment of INRs in part 1 for patients who had received warfarin within their VTE treatment regimen is also a strength. Although warfarin has already been shown to present significant problems when used in patients with cancer, collecting these data within our institution demonstrated to our medical oncologists the need to improve anticoagulation therapy in the majority of their patients with cancer. The medical oncologists were the same throughout all parts of the study; however, the methods for monitoring and adjusting warfarin therapy varied among medical oncologists. Therefore, the INR data collection was important, because it showed the results of this nonstandardized physician-managed oral anticoagulation therapy.

Finally, the multidisciplinary education and preprinted order forms were vital for this study, because they reinforced the evidence-based guidelines’ recommendation and helped improve adherence to the guidelines in an effort to make this recommendation the standard of care at DCH RMC. In addition, the LMWH on the formulary changed during this study, and the education and preprinted order forms helped eliminate confusion about which LMWH to prescribe to the patients with cancer.

Limitations

The limitations of our study include the possibility of VTE events not accounted for during the initial 5-week post-educational intervention-only segment of part 4. This is believed to be true, because the identification and the reporting of potential patients were exclusively voluntary for the nursing staff.

Furthermore, because of the multiple tasks involved in caring for patients with cancer, as well as the distractions, it is quite possible that some patients were missed, especially because reporting patients with suspected VTE to the principal investigator was not part of the nurses’ daily routine.

Some VTE events could have been attributed to the presence of central venous catheters, which was also viewed as a limitation to the study, because the primary cause of the VTE event was not investigated.

In addition, the indication for warfarin was not investigated; therefore, warfarin therapy could have been for anticoagulation related to conditions such as atrial fibrillation or artificial heart valves. However, these patients were not excluded from our study. Finally, given the limitation of being a hypothesis-generated pilot study with a small sample size, a larger confirmatory study to be conducted over a longer duration of time is warranted.

Conclusions

Our future directions include continued pharmacists’ inventions within the area of VTE in patients with cancer to increase adherence to evidence-based guidelines. This may consist of follow-up educational series for new staff members and reminders for the current staff. Clinical updates should be presented, as appropriate, to keep the staff abreast of the most recent guideline recommendations. This study did not evaluate the impact of changing prescribing patterns on the long-term outcomes of our patients. Therefore, outcome studies evaluating the 6-month duration of LMWH monotherapy is a future direction. These outcome studies should address the clinical validity of adherence to the guidelines’ recommendation and determine whether patients at our institution
experience less bleeding and fewer recurrent VTEs as a result of these educational/intervention efforts. As pharmacists continue to become more prevalent in the clinical setting, it is imperative that we are aware of this high-risk population and of the appropriate treatment. In addition to continued education and interventions to the medical staff, patient education can certainly be performed by pharmacists, because the feasibility of long-term self-injections of LMWH remains a practical issue. This study offers a positive contribution to the practice of pharmacy and supplements the existing literature that demonstrates the impact of clinical pharmacists on patient care.

As pharmacists continue to become more prevalent in the clinical setting, it is imperative that we are aware of this high-risk population and of the appropriate treatment.

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Author Disclosure Statement

Dr Steward, Dr Hamid, and Dr Hooker have reported no conflicts of interest.

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