A Closer Look at the Adult Medicine PRN

Overview of the PRN

The Adult Medicine Practice and Research Network (PRN) is composed of students, residents, fellows, clinical pharmacists, and other practitioners from various adult medicine interest areas, including community, family medicine, internal medicine, geriatrics, and managed care. This diverse group encompasses pharmacists from around the world who practice in inpatient and outpatient settings, academia, and the pharmaceutical industry. With its 1065 members – over 200 of whom are student and resident or fellow members – the Adult Medicine PRN is one of the most well-rounded ACCP PRNs, with each individual bringing his or her own expertise within the adult medicine pharmacotherapy realm to the PRN. Objectives of the PRN include providing a means for communication and informal networking among members, providing quality educational programming at national meetings, using the Internet to facilitate access to timely educational updates and facilitate information exchange among adult medicine pharmacists, and providing opportunities for collaborative research.

The PRN is very active, with many opportunities for professional growth through service on its seven committees: Nominations, Programming, Training and Travel Awards, Internal Affairs, External Affairs, Poster Walk-Rounds, and Practice-Based Research Network (PBRN). The PRN communicates and engages its members most commonly through its website, social media (Twitter: @accpamedprn; Facebook: facebook.com/accpamedprn), and e-mail. The PRN's social media sites are very active, sharing new literature, member spotlights, and ACCP news. Many of the PRN members are leaders in the pharmacy profession who make valuable contributions through article publications, poster presentations, and platform presentations at local, state, and national meetings. In the October 2017 *PRN Report*, 6 PRN members had received promotions, 17 had received various honors and awards, 2 had been inducted as new ACCP Fellows, 2 had received grant funding, and 20 had been published. The PRN is proud of its members' accomplishments and strives to highlight these in its annual reports and biannual newsletters to recognize members' diligent efforts to advance both adult medicine pharmacy practice and the profession.

Opportunities and Resources for Students, Residents, and Fellows

The Adult Medicine PRN has a large cohort of resident, fellow, and student members and supports their active involvement in the PRN. Student, resident, and fellow members are encouraged to serve on the PRN's committees, many of whom currently do so.

To encourage professional growth and networking, the PRN sponsors two $500 travel awards for residents, students, or fellows to attend the ACCP Annual Meeting. These awards also allow students and residents to present their scholarship in the form of a platform presentation at the annual PRN business meeting. At the Annual Meeting, the PRN business meeting provides an opportunity to engage all student, resident, and fellow members in networking opportunities. The PRN also recently initiated a roundtable event during the business meeting, which allows students and residents to engage in discussions with clinical specialists and faculty members about various aspects of career development and successful attainment of career goals. During the first roundtable, 6 clinical pharmacists and faculty members and more than 15 students and residents participated.

In addition to articles in the PRN's biannual newsletter, which resident, student, and fellow members can contribute to, the PRN recently started a monthly electronic journal club. This has allowed for experience and practice in presenting in a virtual setting and updating PRN members with clinically important topics. An example of a recent written summary by a participating resident and mentoring clinical pharmacist is included in the article on edoxaban that follows. Students will have the opportunity to share in this experience this summer by presenting interesting patient cases from APPE rotations, which will in turn facilitate professional growth in the future generation of clinical pharmacists.

Clinical Issue

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism (Hokusai VTE Cancer)

Background

Anticoagulation for patients with cancer is a difficult balance of efficacy, safety, feasibility, and patient preference that is commonly encountered because of the increased risk of venous thromboembolism (VTE) in this population. Cancer increases the risk of VTE because of the increased release of procoagulant tissue factor and release of inflammatory cytokines that increase the activation of the clotting cascade. Patients with cancer are also at an increased risk of clot development that varies depending on cancer type, cancer stage, performance status, medical comorbidities, and treatment.[1]

The 2016 *CHEST* guidelines recommend low-molecular-weight heparin (LMWH) for cancer-associated venous thromboembolism (CAT).[2] The recommendation for LMWH over other anticoagulants such as warfarin is the result of the CLOT trial. The CLOT trial was a prospective, open-label trial of patients with CAT who were treated with warfarin (goal INR 2–3) or dalteparin. The results showed a decrease in recurrent VTE at 6 months in the dalteparin group (8%) compared with the warfarin group (15.8%) that was statistically significant (HR 0.48; 95% CI, 0.30–0.77; p=0.002). In addition, the trial found no difference in major bleeding.[3] Although the CLOT trial was limited by a 46% time in therapeutic range within the warfarin group, the trial established LMWH as first-line treatment for CAT.

However, since publication of the CLOT trial, the direct oral anticoagulants (DOACs) have been approved for VTE and offer advantages over LMWH, including minimizing injections and offering some of the same advantages as LMWH over warfarin, including no need for monitoring, less dependence on nutritional status, and simplified dosing regimens. The original trials in which the DOACs were studied for VTE included a small percentage of patients with active malignancy.[4-7] Therefore, the place of DOACs in CAT therapy is unclear.

Hokusai VTE Cancer Trial Summary

Background and Methods

The objective of the Hokusai VTE cancer trial was to compare edoxaban with dalteparin in treating CAT.[8] In this prospective, randomized, open-label noninferiority trial, patients were randomized to receive either edoxaban 60 mg by mouth daily after a 5-day LMWH lead-in or dalteparin 200 units/kg/day for 1 month, followed by dalteparin 150 units/kg/day. Patients in the edoxaban arm had the dose reduced to 30 mg by mouth daily if their CrCl was 30–50 mL/minute/1.73 m^2, if their weight was less than 60 kg, or if they were receiving a concomitant P-glycoprotein inhibitor.

Patients were included in the study if they were 18 years or older, had symptomatic or incidental findings of deep venous thrombosis (DVT) or pulmonary embolism (PE), and had active cancer. Patients were excluded if the active malignancy was basal or squamous cell carcinoma of the skin, had an Eastern Cooperative Oncology Group (ECOG) score of 3 or 4, if their CrCl was less than 30 mL/minute/1.73 m^2, if they had been pretreated with anticoagulation for more than 72 hours, if they had liver injury or chronic liver disease, if their platelet count was less than 50,000/mm^3, if they had uncontrolled hypertension, if they had chronic use of nonsteroidal anti-inflammatory agents, if they took aspirin greater than 100 mg/day or dual antiplatelet therapy, or if they were treated with a strong P-glycoprotein inhibitor.

The primary outcome was the composite of recurrent VTE and major bleeding. Major bleeding was defined as bleeding at a critical site, bleeding that required transfusion of 2 or more units of packed red blood cells, bleeding that resulted in a hemoglobin decrease of 2 mg/dL or more, or bleeding that contributed to death. Secondary outcomes included recurrent VTE, recurrent DVT, recurrent PE, major bleeding, nonmajor bleeding, and death. The study was designed as a noninferiority trial with respect to the primary outcome. Delta was set at 1.5, designating the upper limit of the 95% confidence interval to

be less than 1.5 to determine the noninferiority of edoxaban to dalteparin with respect to the primary outcome.

Results

Baseline characteristics were similar between the treatment groups with respect to age, sex, weight, ECOG performance status, and risk factors for bleeding. Twenty-three percent of patients within the edoxaban treatment arm had the dose reduced to 30 mg by mouth daily. Patients in the edoxaban arm had a median therapy of 211 days (interquartile range 76–357), and patients in the dalteparin arm had a median therapy of 184 days (interquartile range 85–341), which was significantly shorter (p=0.01).

The primary outcome of recurrent VTE or major bleeding occurred in 67 of 522 patients (12.8%) in the edoxaban arm compared with 71 of 524 patients (13.5%) in the dalteparin arm (HR 0.97; 95% CI, 0.70–1.36) (Table 1). Edoxaban was noninferior (p=0.006) but not superior (p=0.87) to dalteparin with respect to the primary outcome. Recurrent VTE was lower in the edoxaban arm than in the dalteparin arm, largely because of a statistically significant reduction in recurrent DVT in the edoxaban arm (Table 1). An increase in major bleeding with edoxaban (6.9%) compared with dalteparin (4.0%) was statistically significant (HR 1.77; 95% CI, 1.03–3.04; p=0.04) (Table 1). In a subgroup analysis of major bleeding, GI bleeds were higher in the edoxaban group (3.8%) than in the dalteparin group (1.1%).

Table 1. Results of Clinical Outcomes of Recurrent VTE and Major Bleeding in Hokusai VTE Cancer Trial

Outcome – No (%)	**Edoxaban (n=522)**	**Dalteparin (n=524)**	**Hazard Ratio (95% CI)**	**p value**
Recurrent VTE or major bleeding at 12 mo or trial end	67 (12.8)	71 (13.5)	0.97 (0.70–1.36)	0.006[a] 0.87
Recurrent VTE	41 (7.9)	59 (11.3)	0.71 (0.48–1.06)	0.09
Recurrent DVT	19 (3.6)	35 (6.7)	0.56 (0.32–0.97)	
Recurrent PE	27 (5.2)	28 (5.3)	1.00 (0.59–1.69)	
Major bleeding	36 (6.9)	21 (4.0)	1.77 (1.03–3.04)	0.04
Clinically relevant nonmajor bleeding	76 (14.6)	58 (11.1)	1.38 (0.98–1.94)	
Death from any cause	206 (39.5)	192 (36.3)	1.12 (0.92–1.37)	

a. p value for non-inferiority

Discussion

Although edoxaban was noninferior to dalteparin, this study had several limitations, making it difficult to apply the study to clinical practice. The study was designed to determine noninferiority on the basis of a composite outcome that included both safety and efficacy. Use of a composite safety and efficacy end point is unprecedented in anticoagulation trials, resulting in difficult interpretation and indeterminate application. The study was powered with a sizable delta of 1.5 for the upper limit of the 95% confidence interval. The upper limit for noninferiority was determined on the basis of clinical opinion and not solidified in the previous literature as an acceptable upper limit. The potential for a 50% increased risk of either a recurrent VTE or a major bleeding event would have to be outweighed by the benefit of using an oral agent. The authors also note that study limitations include the open-label trial design and the lower-than-expected number of primary outcome events.

The rates of recurrent VTE in the Hokusai VTE cancer trial (edoxaban 7.9%, dalteparin 11.3%) are similar to the rates of recurrent VTE in the CLOT trial (warfarin 15.8%, dalteparin 8%). The decrease in recurrent VTE with both dalteparin and edoxaban compared with warfarin is primarily due to of the prevention of DVT. The comparison shows that edoxaban can be considered noninferior to LMWH in efficacy for preventing recurrent VTE in patients with active malignancy. The major bleeding rates in patients treated with dalteparin in the Hokusai VTE cancer trial (edoxaban 6.9%, dalteparin 4.0%) are similar to those in the CLOT trial (warfarin 3.6%, dalteparin 5.7%). The risk of major bleeding was greater in patients treated with edoxaban than in patients treated with dalteparin and warfarin.[2] These comparisons are further supported by a recent meta-analysis. The meta-analysis by Li et al. shows a potential for decreasing the risk of recurrent VTE with DOACs compared with LMWH (RR 0.65; 95% CI, 0.42–1.01); however, the analysis also shows a greater risk of bleeding with DOAC use than with LMWH (RR 1.74; 95% CI, 1.05–2.88).[9] In conclusion, edoxaban is noninferior to dalteparin in preventing recurrent CAT; however, edoxaban may increase the risk of major bleeding compared with dalteparin. The bleeding events are primarily GI. The DOACs should be used in caution in patients with a history of GI bleed, GI cancers, or liver metastases.

<u>Practice Implications</u>

Publication of the Hokusai VTE cancer trial adds to the growing evidence for DOAC use in CAT. Previous literature for DOACs in CAT was limited by retrospective design and sample size. Given the noninferiority trial design and the findings of no difference in recurrent VTE but the increase in major bleeding, the place of DOACs in therapy is still unclear. The 2018 National Comprehensive Cancer Network guidelines recommend LMWH as the preferred agent for CAT, but also recommend DOACs for patients who refuse or have a compelling reason to avoid LMWH.[10] The current literature supports the use of DOACs as reasonable second-line options, similar to warfarin, in CAT.

<u>Follow-up Questions:</u>

(1) How have these updates in literature and guidelines changed practice style?

The practice at my current institution is to continue use of LMWH as the preferred agent for CAT. There has been an increased comfort in continuing DOACs in patients who have previously taken DOACs and have a newly diagnosed malignancy. There is also increased use of DOACs in patients who refuse injections. Overall, there is a significant component of patient choice and education of patients about the risk-benefit of each therapy. Including the patient also allows for inclusion of his or her goals of care. There is now more evidence to include in that conversation when explaining risk-benefit.

(2) Are there particular malignancies for which you would avoid DOACs?

Use of DOACs in malignancies that are high bleed risk would be of greatest concern. The increased rate of major bleeding in trials has primarily been GI bleeds. Use of DOACs should be avoided in primary GI

malignancy and in cancer that involves GI or liver metastasis. Another malignancy that would be of concern because of the risk of bleeding is any malignancy involving the brain or central nervous system.

(3) Why is there an increased risk of GI bleed in the DOAC CAT literature? How does this relate to previously published literature for DOAC use in treating VTE?
The landmark trials for DOAC use in treating VTE have low overall bleeding rates. The GI bleed rates are 0.3%–0.4% of patients treated in the trials. Overall, GI bleed rates are higher with dabigatran than with warfarin, equivalent with rivaroxaban and edoxaban compared with warfarin, and lower with apixaban than with warfarin. Extrapolating these data for comparing DOACs with LMWH is difficult. The rates of GI bleed in the Hokusai VTE cancer trial were likely increased because over 20% of the patients in the trial had GI malignancies. The GI bleed rates in the edoxaban and dalteparin arms were 3.8% and 1.1%, respectively. Overall, the increase in GI bleed is not surprising, given the data compared with warfarin and the baseline characteristics of the patients within the trial.

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Journal article summary submitted by: Leslie Wooten, Pharm.D.; Jamie Sebaaly, Pharm.D., BCPS; and Ryan D'Angelo, Pharm.D., B.S., BCPS